Assessment of Frailty and Quality of Life in Octogenarians With symptomatic Coronary artery disease.

The FRAIL HEART Study

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ABSTRACT

BACKGROUND:

Symptomatic coronary artery disease (CAD) is an increasing problem for older adults, however little is known about the relationship between frailty and health outcomes.

PURPOSE:

To determine the prevalence of, and relationship between frailty, quality of life (QoL) and major adverse cardiac events (MACE) in older adults with CAD.

METHODS:

A narrative literature review confirmed a knowledge gap. We therefore conducted an exploratory, prospective observational study of in- or out-patients (≥80years) with symptomatic CAD recruited between June 2016 and January 2017. Participants were evaluated for frailty (Fried Frailty Phenotype, Edmonton Frailty scale), quality of life (QoL; SF-12), clinico-demographic characteristics, including treatments received. Data were collected at baseline and 4 months and descriptive statistics applied. Regression techniques were used to explore relationships between variables.

RESULTS:

Consecutive participants (n=150; mean age 83.7±3.2 years; 99 (66%) men; acute coronary syndrome 82 (54.7%)) were treated with: PCI (51; 34%); CABG (15;10%); medical (84; 56%). About one quarter were frail (26% EFS; 28% FFP). Frailty was inversely related to SF-12 (PCS 30.5±7.1 vs 43.5±7.6, p=0.005, MCS 47.4±i12.8 vs 57.1±6.4, p=0.003) and directly related to comorbidity (7.5±2.4 vs 5.9±1.6, p=0.005) at baseline. Follow up at 114 days (50-243) showed overall MACE (24.7%) and poorer survival amongst frail participants (Dead/frail 50.0% versus alive/frail 26.2%, p=0.002).

CONCLUSIONS:

About one quarter of older adults with CAD have frailty. Our data show that frailty is inversely related with QoL and clinical outcomes. This data suggest that frailty is an important therapeutic target in this age group. A larger cohort is needed to confirm these exploratory findings.

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AUTHOR'S DECLARATION

'I confirm that this work is original and that if any passages or diagrams have been copied from academic papers, books, the internet or any other sources these are clearly identified by the use of quotation marks and the references are fully cited. I certify that, other than where indicated, this is my own work and does not breach the regulations of HYMS, the University of Hull or the University of York regarding plagiarism or academic conduct in examinations. I have read the HYMS Code of Practice on Academic Misconduct, and state that this piece of work is my own and does not contain any unacknowledged work from any other sources'. 'I confirm that any patient information obtained to produce this piece of work has been appropriately anonymised'.

Dr S Qayyum

STROBE STATEMENT CHECKLIST:

	Item No	Recommendation
Title and abstract	1	See Cover page and Abstract which follows the title page.
Introduction		
Background/rationale	2	The scientific background and rationale had been discussed in Chapter1, 2 and 3
Objectives	3	Study objectives are outlined in section 4.3
Methods		
Study design	4	Study design is outlined in section 4.1
Setting	5	Setting, locations, periods of recruitment, follow-up, and data collection are described in Chapter 4.6
Participants	6	(*a*) Eligibility criteria, recruitment process, methods and follow up are described in section 4.4, 4.7
		(*b*) This was not a matched study.
Variables	7	See section 4.8
Data sources/ measurement	8*	See section 4.7
Bias	9	Study Limitation are described in 3.4
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Study Results		
Participants	13*	(a) The number of study participants at each stage are stated in section 5.3.1,5.3.3, 5.3.5,6.3.1, 6.3.3, 6.3.5, 7.2
Descriptive data	14*	(a)Clinical and frailty characteristics of the participants at each stage have been described

		in sections 5.3.1, 5.3.3, 5.3.5, 6.3.1, 6.3.3,6.3.5, 6.3.6.
		(b) Participants loss to follow up are discussed in section 6.3.1,6.2.4,
		(c) Average follow up time is described in section 6.3.1, 6.3.2
Outcome data	15*	Number of outcome events have been described in section 6.3.13, 6.3.17, 5.3.10, 6.3.7
Main results	16	Main results at Baseline are reported in chapter 5 section 5.3 onwards
		Results at Follow up are reported in Chapter 6 section 6.3
Other analyses	17	A number of analyses besides the main result were carried out to understand the data better. They are described in Chapter 5, 6 and 7.
Discussion		
Key results	18	Results are given in section 5.3, 6.3 and 7.3. Due to a large number of sub-analysis each results are discussed after each analysis and again at end of the chapter.
Limitations	19	Overall limitations of the study are discussed in section 3.4
Interpretation	20	The results have interpreted after each analysis in section 5.3, 6.3, 7.3
Generalisability	21	See overall discussion at end of Chapter 5, 6,and 7
Other information		
Funding	22	The study did have a small grant from Hull and East Riding Cardiac fund to cover blood test costs.

1 CHAPTER- CORONARY REVASCULARISATION IN AN AGEING POPULATION.

1.1 INTRODUCTION

With the advances in medical therapeutics and preventive medicine there has been a demographic shift in the population living in the developed world. People are living longer than before. According to the office of national statistics estimates for 2014, there are 6.4 million (4.8% of total population) people above the age of 80 years living in UK(1). This number is expected to rise to 7.4 million by 2039 as per population growth projections representing 8.4% of the total UK population. This makes older adults the most rapidly expanding age group of the UK. Similar trend has been noted across all the developed countries of the world. This increase in the numbers of older people means that by mid-2039 more than 1 in 12 of the population is projected to be aged 80 or over(2).

1.2 BURDEN OF CORONARY DISEASE IN THE OLDER ADULTS.

In this aging population, besides other comorbidities, coronary artery disease is increasingly prevalent (see figure 1-1). According to cardiovascular statistics published by British Heart Foundation in 2013, the prevalence of angina is estimated around 16.96%, myocardial infarction is 12.08% and heart failure is 7.84%, in population above 75 years of age(3, 4). In octogenarian population, the American Heart Association suggests an even higher prevalence of coronary disease, 34.6% in

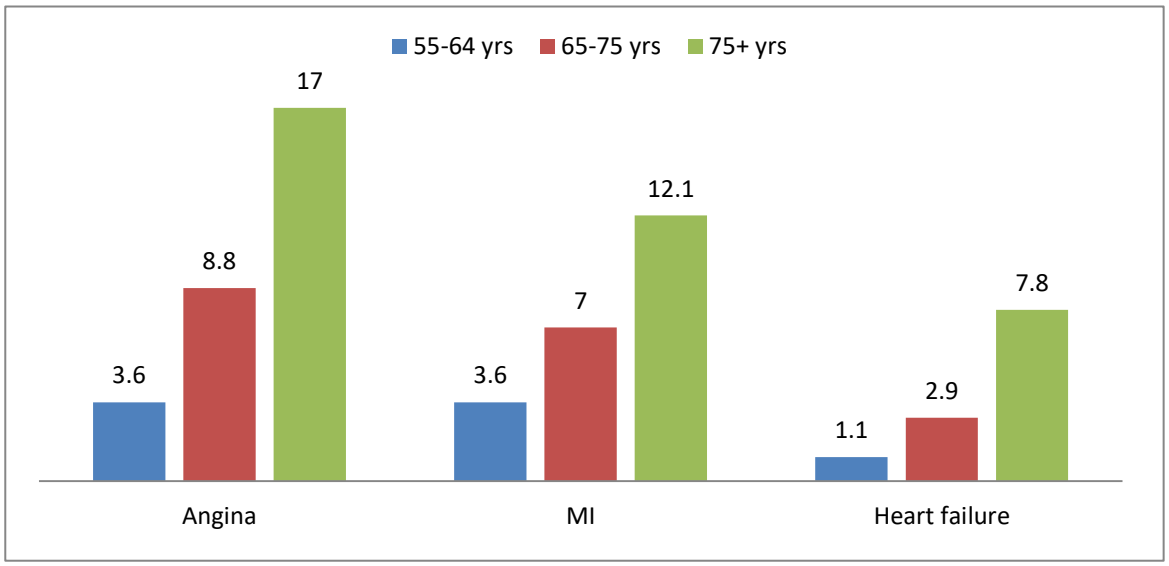

Figure 1-1: Prevalence (%) of cardiovascular disease as per decade in 2013. Derived from estimates in cardiovascular statistics UK, published by British Heart Foundation in 2014.

males and 18.6% in females(5). The incidence of angina is 9.3 per 100 person years in males and 3.5 per 100 person years in females between the ages of 75 to 84(6). In UK, heart disease remains the leading cause of mortality in males above 80 year of age, while in females of the same age it is the second most common of death. The MINAP (Myocardial ischaemia National Audit Project) national dataset encompasses all the admissions with ACS across United Kingdom. The MINAP data revealed that older adults formed a substantial proportion of the admissions with ACS. 36.8% of the patients were more than 75 years of age and 11.9% of the patients were more than 85 years of age(7). It suggests that older adult patients present more with NSTEMI rather than STEMI and ACS are more prevalent in males. According to MINAP 2019 report, in octogenarians the prevalence of NSTEMI was around 7.5% in males and 6.0% in females while prevalence of STEMI was 2.7% in males and 2.5% in older females(8).

This reflects the high burden of cardiovascular disease in the older adult population. It is likely that this burden of cardiovascular disease will increase in future. Management of cardiovascular disease in older adults poses its own unique challenges and complexities. They often have more advanced disease with multi-vessel involvement and higher calcium scores making percutaneous coronary intervention (PCI) more challenging. In addition, they may have multiple comorbid conditions. These factors should be taken into consideration when deciding on the optimal management strategy as they are at increased risk of procedural complications. .

Having recognised the increasing prevalence and burden of coronary artery disease in the older population, a literature review was undertaken to appraise the evidence for revascularization in this population and highlight issues peculiar to this age group.

1.3 INCREASED MORTALITY IN OLDER ADULT PATIENTS WITH MYOCARDIAL INFARCTION.

The older adult population have more advance coronary artery disease with multiple vessel involvement and calcification. This usually co-exists with multiple comorbidities. This makes older patients with symptomatic coronary artery disease a high risk group overall. These risk need to be taken into consideration at time of deciding optimal management strategy for their coronary artery disease.

The incidence of STEMI (ST Elevation Myocardial Infarction) increases with age and accounts for around 30% of ACS cases above 75 year of age. The incidence of LBBB (Left Bundle Branch Block) also increases with age. In NRMI (National Registry of

Myocardial Infarction) registry LBBB was found in 33.8% of patients with STEMI above 85 years of age(9). In the GUSTO-1 trial, the 30 day mortality after STEMI was 10 times higher in patients more than 85 years of age compared to their younger counterparts (30.3% versus 3%)(10). The incidence of stroke after MI also increases with age. The overall stroke rate after STEMI is less than 3% in older patients above 85 year of age. Older patients have a 1 in 25 chance of being hospitalised with a stroke after presenting with an acute MI(9, 11).

In patients presenting with NSTEMI, likewise, the inpatient mortality rate increase progressively with advancing age. Younger patients less the 65 years of age have 1 in 100 chance of dying during their hospitalisation with an NSTEM but this risk increases to 1 in 10 in patient over 85 year of age(9). The chance of dying at one year after NSTEMI is about 1 in 5 in patients over 75 years of age and 1 in 4 for those over 85 years of age. The Global Registry of Acute Coronary Events (GRACE) is an international registry designed to track in-hospital and long term outcomes in patients presenting with ACS over 250 hospitals across 30 countries. The 1 year mortality rate from GRACE registry was 15% in 75-85 year age group and 25% in above 85 year age group(12). Similarly, incidences of complications after NSTEMI also increase with age.

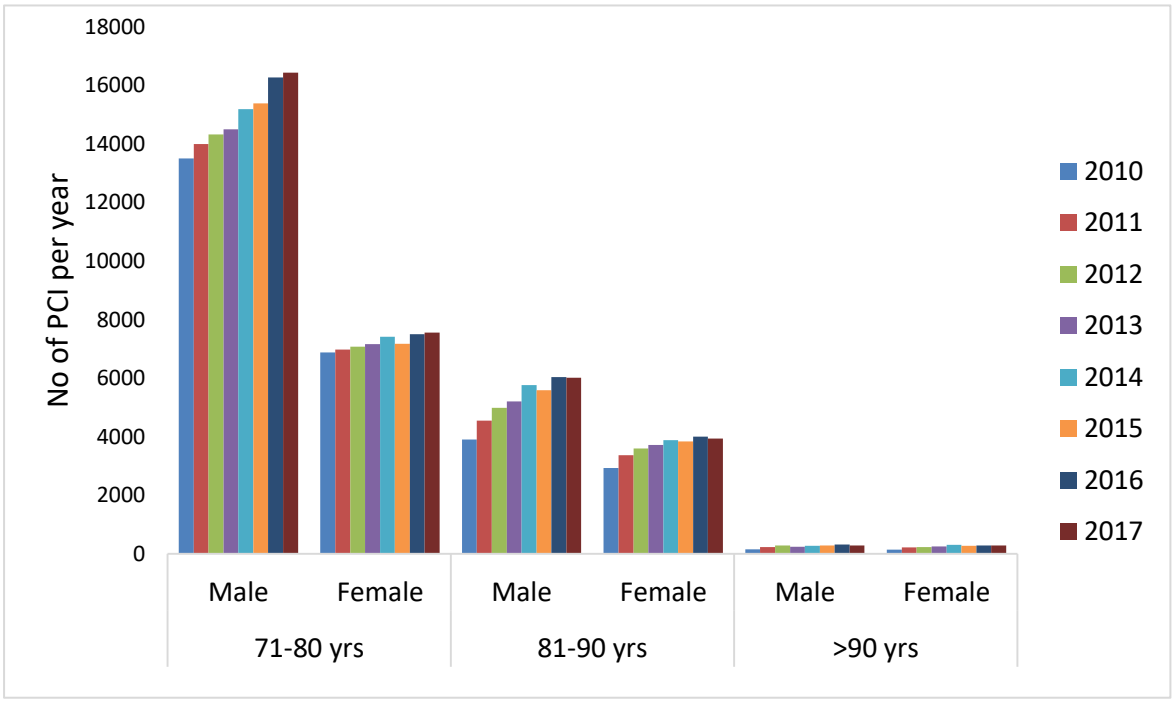

Figure 1-2: Number of percutaneous coronary intervention (PCI) per year in UK age and gender distribution. Data source was from BCIS audit available at www.bcis.org.uk

1.4 INCREASING TREND OF CORONARY INTERVENTION IN THE OLDER ADULT POPULATION

This increase in prevalence of coronary artery disease has led to a steady increase in the number of percutaneous coronary intervention being performed in the older population. BCIS (British Cardiovascular Intervention Society) audit data has shown a yearly increase in number of procedures being performed in patient above 80 years of age (Figure 1-2). In 2014, 10.6% of the PCI were performed in patients above 80 years of age(13). Patients above 80 years of age constitute around 12.8% of the primary PCI done per centre. In the USA, approximately 25% of all the PCI are performed in patients over 75 years of age, 12% being in octogenarians (14).

1.5 RATIONALE FOR REVASCULARISATION WITH PERCUTANEOUS CORONARY INTERVENTION IN THE OLDER ADULTS.

The rationale for revascularisation in the older adult population is mainly derived from subgroup analysis of studies performed on much younger population mostly with normal LV function, few co-morbidities and no previous history of revascularisation. Most of the large percutaneous coronary intervention trials have concentrated more on the younger population while older patients have been poorly represented or excluded(15). Dodds et all conducted a review of eighty clinical trials of ACS between 2007 and 2009, a total of 68016 patients were recruited in these trials, however only 13,8% of the study participants were ≥ 75 years of age whereas the overall prevalence of ACS in the same age group was estimated around 41.9%(16).Trial enrolment of patients aged 75 years and older increased from 2% during 1966-2000 to 9% during 1991-2000 and around 11% during the last decade but remains well below their actual representation among all patients with myocardial infarction (37% in the USA and 40% in UK)(15, 16). In clinical practice where older adult patients may have multiple co-morbidities, the results of these studies cannot necessarily be extrapolated and it is therefore extremely difficult to decide on the optimal approach for the management of this high risk group. Although available data does suggest that revascularisation can be performed safely in older adult patients, with acceptable short- and mid-term outcomes, the level of evidence is low and the population highly selected. Most of the evidence for PCI is derived from registry based observational studies hence lacking a control group. Registry derived data presents real life data but is inherently biased as it does not take into account patients who do not undergo PCI.

There are only a few randomised control trials concentrating on this population group especially comparing with medical therapy. The TIME Trial (The Trial of Invasive versus Medical Therapy in Elderly Patients with Chronic Symptomatic Coronary Artery disease) is among the few early randomised controlled trials performed in older adult population with chronic angina(17). Older patients above eighty years age, with chronic stable angina despite two antianginal medication were randomised to an invasive (n=153) or optimised medical therapy (n=148). After initial 6 month, results suggested an improvement in symptoms, quality of life and reduction in adverse cardiac events in the group that was treated invasively with PCI. However, the one and four year follow up showed no significant difference in symptoms, quality of life and survival between the two groups(18). The difference in the adverse cardiac events was mainly driven by hospital admissions for ACS which was taken as part of composite defining adverse cardiac event. There was no significant difference in mortality at 4 years between the groups.

This study definitely highlights the need for focused high quality randomised control trials in this population to determine the optimum management of their coronary artery disease. ISCHEMIA trial (Initial Invasive or Conservative strategy for Stable Coronary Disease) is a landmark study published this year addressing management of stable angina comparing conservative management to early invasive strategy for stable angina. However the average age of the study participant was 64 years with maximum age of 70(19). There are a few upcoming trials looking specifically into management of coronary artery disease in older adult population. RINCAL (Revascularisation or medical therapy in elderly patients with acute angina syndromes) trial is a UK based randomised controlled trial comparing outcomes of optimised medical therapy and optimised medical therapy plus coronary intervention in older patients above 80 years of age presenting with acute coronary syndrome. The results of the trial are eagerly awaited. Similarly, SENIOR-RITA (Older Patients with Non-ST SEgmeNt elevatIOn myocaRdial Infarction Randomized Interventional TreAtment Trial) Trial is a multicentre prospective trial looking specifically at patients more than 75 years of age with NSTEMI randomised to invasive and conservative treatment strategies. It is in recruitment phase at present.

The risks associated with PCI in older patients have fallen with the introduction of newer devices and techniques such as the use of drug-eluting stents (many of which do not require very long duration of dual anti-platelet therapy), use of radial artery access

in preference to femoral(20), as well as the more widespread use of calcium modification devices such as the Rotablator (Boston Scientific Corp, Malborough, USA) and intravascular lithotripsy (Shockwave Medical Inc, Carlifonia, USA). Despite a trend of reducing risk of complications , Registry data still indicate higher 30 day and 1 year mortality rates compared to PCI in younger patients(21, 22). A systematic review and meta-analysis of 66 studies of PCI in octogenarians has been published. This included studies of both stable angina as well as acute coronary syndromes and found the mortality to be 5.4% at 30 days increasing to 13% at 1 year(23).

1.6 OLDER ADULTS WITH ACS AS AN UNDERTREATED GROUP

Older patients admitted to hospital not only have high in-hospital mortality rate but are also less likely to receive evidence based treatment(12). This has led to quality care programs to focus on deficit in care in this age group. Gale et al(7) analysed the MINAP data from 2003 to 2010 and reported a year on year reduction in in-hospital mortality in older age group but concluded that biases still remain in ACS care in the older adults. They continue to have prolonged hospital stay and higher in-hospital mortality rates(24). It was also noted that older patients were less likely to make their own way to the hospital. They were more likely to have ACS while in hospital with other illnesses compared to younger age group patients. This can lead to delay in their treatments predisposing them to adverse or poor outcomes. Furthermore older patients with ACS are less likely to be admitted to cardiac care unit or cardiology ward or be under the care of cardiologist despite the fact that they had the highest prevalence of cardiogenic shock among all age groups. Among patients presenting with STEMI older patients were less likely to undergo primary PCI (15.1% vs 24.3%) or thrombolysis (2.4% vs 11.8%)(7). Several factors have been suggested for this lack of primary intervention in older adult patients. Some authors have suggested reluctance on physician part with perception of poor outcomes, low procedure success and high complication rates(25).

1.7 AGE RELATED PATHOPHYSIOLOGICAL FACTORS AFFECTING PCI OUTCOMES IN OLDER ADULT POPULATION.

With advancing age several pathophysiological changes occur in the body which makes percutaneous coronary intervention in this age group more challenging.

1.7.1 ADVANCED CORONARY ATHEROSCLEROSIS

Atherosclerosis is an age related process. Vascular aging in human is characterised by luminal dilatation, intimal and medial thickening, vascular stiffening and endothelial

dysfunction(26). Above 80 years of age 80% of the patients have evidence of coronary artery atherosclerosis compared to 50% in middle aged patient. With advancing atherosclerosis there is compensatory dilatation and stiffening of the coronary vessel(27). The coronary artery calcification scores are universally high in older patients hence limiting the value of calcium scoring in this age group(27). Octogenarians have higher prevalence of calcified lesions, tortuous coronary vessels, ostial disease, left main stenosis and multi-vessel disease(22).

The risk of octogenarians undergoing contemporary PCI are two to four fold higher than their younger counterparts(28). On coronary angiography, the anatomical complexity can be assessed using a validated score called the SYNTAX score. The SYNTAX trial(29) demonstrated that patients with a high SYNTAX score should be considered for CABG in preference to PCI, with lower mortality and complete revascularisation. Studies on ACS in older population have shown up to 30.7% participants having SYNTAX score more than 23(30). This suggests that a considerable proportion of older adult patients have surgical coronary disease.

1.7.2 HIGH BLEEDING RISK AND ALTERED HAEMOSTATIC MECHANISMS

There is an increased incidence of arterial thromboembolism in the older population, which paradoxes with increased risk of bleeding as well. Aging is associated with increased levels of plasma fibrinogen, factor VII and factor VIII which have been shown to increase risk of thrombosis. An augmented response of platelets to different aggregating stimuli has been demonstrated in the older population(31). Also elevated level of beta-thromboglobulin and increased production of thromboxaneA2 has been reported. Fibrinolytic activity is also impaired in the older adults probably due to increase level of tissue plasminogen activator. All of these factors put older patients at relatively increased risk of thrombosis.

However, advancing age is an independent predictor of bleeding and major bleeding is independently associated with mortality following PCI. All patients with CAD, particularly those treated with stent implantation, require anticoagulant therapy at the time of the procedure and are then prescribed anti-platelet therapy. Analysis of GRACE registry data showed that the frequency of major bleeding is 6.8% after ACS in patients over 80 years of age compared to 2.6% in patients 60 years of age and under(32). Contemporary studies using trans radial approach have cited a much lower bleeding

risk in older patients (0.77% vs 0.34%) but still significantly higher than the younger population(33). Major bleeding after PCI is associated with increased adverse outcomes and increased risk of death and stroke in the older population(34). The exact explanation of this association is unclear but several mechanisms have been hypothesized including hypovolemia, anaemia, hypotension and decrease oxygen carrying capacity due to acute blood loss would be obvious explanation. Sub-analysis of ACUITY (Acute Catheterisation and Urgent Intervention Triage strategY) trial data set showed six times more in-stent thrombosis in patient who bled most likely due to early discontinuation of antiplatelet therapy in these patients (35).

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1.7.3 AGE RELATED CARDIOVASCULAR PHYSIOLOGICAL CHANGES

With age, the walls of the large arteries become stiffer due to intimal and medial thickening. This is accompanied with luminal dilatation and endothelial dysfunction which leads to a rise in the systolic and a fall in diastolic pressure (26, 36). Low diastolic pressure is associated with low coronary artery flow. Elevated pulse pressure is in itself independent risk factor for future cardiovascular events(37). With advancing age there is a trend towards increase in left ventricular thickness, changes in diastolic filling patterns, impaired left ventricular ejection, decreased heart rate reserve capacity and increased altered heart rhythm like atrial fibrillation. These physiological changes reduce the cardiac reserve and in older patients can affect the outcome or prognosis of acute disease related challenge to the heart(26).

Endothelial dysfunction plays a major role in the promotion of atherosclerosis. Advancing age is associated with downregulation of endothelial nitric oxide, nitric oxide synthase as well as endothelial prostacyclin(38). Recent studies have suggested incomplete endothelial reconstitution following vascular injury and negative remodelling of the coronary vessel in the older adults. This has been attributed to age related decrease in endothelial progenitor cells and impaired mobilisation of the progenitor cells to sites of vascular injury(39, 40)A delay in the process of endothelial recovery is a known risk factor for late stent thrombosis(41).

1.7.4 MULTIMORBIDITY AND FRAILTY

Because of accumulation of co-morbid conditions, age is a significant predictor of outcomes after revascularisation. As patients get older, this risk is further increased as they accumulate comorbidities. There is higher incidence of chronic kidney disease in

the older adult population which adversely affects the peri-procedural and long term outcomes after PCI and CABG surgery(42). Over half or the older adults above 75 years age are living with three or more chronic condition(43). These make older patients a high risk group and most of the risk prediction scores like EuroSCORE and STS score, will take this into account by giving extra score to advancing age. EuroSCORE (European System for Cardiac Operative Risk Evaluation) and STS (Society of thoracic surgeons) are risk scores that predicts the risk of operative mortality after cardiac surgery. There is evidence that these scores significantly overestimates the mortality risk when used in older octogenarians (44, 45).

Frailty is quite prevalent in older age group and even more in patients with cardiovascular disease. In community dwelling population the prevalence of frailty has been reported as 9.5% in over 75 years which increases to 25% over 85 years age(46). Frailty is associated with increased mortality and morbidity and is an independent predictor of post procedural outcomes like falls, development of disability, prolonged hospitalisation and institutionalisation (36, 47). Frailty has been associated with increased 30 day and one year mortality after PCI and predicts length of hospital stay independent of age, gender and comorbidities(48).

1.7.5 DIFFERENTIAL PHARMACOKINETIC RESPONSE AND EFFECTS OF DUAL ANTIPLATELET THERAPY IN ELDELY

Decreased volume of distribution and reduced creatinine clearance leads to significant changes in drug efficacy and concentration in older adults. Glomerular filtration rate should be used to assess renal function as serum creatinine levels may fall with decreasing muscle mass with age(49). Drug clearance can also be compromised with advancing age due to decrease in liver mass, hepatic blood flow and liver cytochrome P450 activity(36). Due to increase age related bleeding risk and altered pharmokinetics the older patients are at predisposed at adverse effects of antiplatelet therapy which are a cornerstone of ACS drug therapy.

1.8 EVIDENCE BASE FOR PCI IN OLDER PATIENTS

Older patients with coronary artery disease are a higher risk group for whom revascularisation can offer symptomatic if not prognostic benefit. There is so much heterogeneity across this age group that a “one size fit all” approach is not feasible in older population (9).

1.8.1 ADVERSE OUTCOME PREDICTORS FOR PCI IN OLDER PATIENTS

Evidence suggests a higher mortality and MACE (Major Adverse Clinical Event) incidence in older age group. Multivariate analysis New York State Angioplasty registry suggested the following strongest correlates of short term mortality (28, 50). These included older patients undergoing both elective and emergency PCI across the whole spectrum of ACS

1) Cardiogenic shock
2) Age>80yrs
3) Hemodynamic instability
4) Cardiopulmonary resuscitation
5) Renal failure
6) Current heart failure
7) Myocardial infarction less than 24 hours
8) Multi-vessel coronary artery disease
9) Peripheral vascular disease

1.8.2 PCI IN OLDER PATIENTS WITH STEMI

There is limited evidence available about the benefit and efficacy of primary PCI in the older population. Most of these studies refer to select patients rather than consecutive and unselected patients (51). Furthermore the studies comparing primary PCI and Fibrinolytic therapy have only a small proportion of patients over 75 years of age (52).The generalization of the results of these trials to the real life should be done with caution and within limitations(9). Subset analysis of PCI versus thrombolytic therapy trials suggest PCI to be the preferred reperfusion strategy in the older population. Primary PCI even in this age group has been related to fewer in-hospital deaths, reduced mortality and recurrent MI compared to thrombolysis(53). Early contemporary thrombolytic therapy may be an alternative to no reperfusion, when PCI is not available or contraindicated. This has been demonstrated in trials and registries alike in patients up to 85 years of age. The incidence of intracranial haemorrhage after Fibrinolytic therapy is 1.5% overall and 2.9% in the very elderly above 85 years of age (54).Evidence from small randomised trials support primary PCI as the better reperfusion therapy in older patients presenting with STEMI (55-57). The Global Registry of Acute Coronary Events (GRACE) sub-analysis of 2975 patients over 70 year of age presenting with STEMI showed lower in hospital mortality rate for primary PCI (OR 0.62, CI 0.39-0.96) compared to thrombolysis(58). GUSTO IIb Trial suggested that older adults were the most to benefit from primary revascularisation strategy compared to other age groups(59). Hence, primary PCI remains the preferred

reperfusion strategy in the older patients presenting with STEMI. The IFFANIAM (impact of frailty and functional status on outcomes in elderly patients with ST elevation MI) study aims to assess patients over 75 years of age presenting with STEMI for baseline functional status including frailty and comorbidities and assess its relationship with one year mortality(60).

1.8.3 PCI IN OLDER ADULTS WITH NSTEMI

A review of high risk NSTEMI older patients enrolled in GRACE registry between 1999 and 2006 showed that revascularisation was associated with reduction in 6 month mortality both in older patients more than 70years (OR 0.38, CI 0.26-0.54) and very old patients over 80 years (OR 0.68, CI 0.49-0.86) of age(61). It was again noted that older patients were less likely to undergo revascularisation. In age subgroup analysis of, Treat angina with Aggrastat and determine Cost of Therapy with an Invasive Strategy-Thrombolysis in Myocardial Infarction 18 (TACTICS-TIMI 18) study early invasive strategy was associated with greater absolute reduction (10.8%) and relative risk reduction (56%) in death and MI at 30 days in patients more than 75 years of age (62). This benefit was associated with increase (17%) risk of major bleeding with intervention. Most of the revascularisation trials were carried out before the times of contemporary intervention. Among the contemporary trials there are only a few that allow subgroup analysis for older age group. British Heart Foundation SENIOR-RITA trial, aims to look at one year outcomes of older patients over 75 years of age presenting with NSTEMI treated conservatively and invasive management strategy. The trial is in recruitment phase at present. The MOSCA-FRAIL (Invasive versus conservative strategy in frail patients with NSTEMI) trial is currently comparing invasive and conservative strategies in elderly frail patients with NSTEMI(63).

1.8.4 PCI IN OLDER ADULTS WITH STABLE ANGINA.

TIME Trial (Trial of invasive versus medical therapy in elderly patients with chronic symptomatic angina) investigators reviewed the benefit of revascularisation over medical therapy in older patients with chronic angina whose symptoms were not controlled with at least two antianginal medications(17). They concluded that patients 75years of age and above benefitted from revascularisation despite optimised medical treatment in terms of symptom relief and improvement in quality of life(64). However, the one and four year follow up showed no significant difference in symptoms, quality of life and survival between the two groups(18).

RANCAL Trial (Revascularisation or Medical Therapy in Elderly Patients with Acute Anginal Syndromes) is looking into comparing optimised medical therapy to revascularisation in older patients above 80 years of age. It is a randomised trial being carried out across multiple sites in UK(65).

1.8.5 DIFFICULTIES IN RISK ASSESSMENT IN OLDER PATIENTS FOR PCI

Risk assessment of older patients undergoing invasive coronary interventions is challenging. More old patients with multiple co-morbid condition presenting with acute coronary syndromes and undergoing PCI. This age group is not well presented in the present risk assessment models where the average age of the patients usually range between 59 and 67 years(66). They were either excluded from the studies due to comorbidities or were present in very small number. In older patients undergoing PCI frailty, comorbidity and poor quality of life are prevalent and associated with adverse outcomes. In a Mayo clinic study of patients undergoing PCI frailty was reported in 18.6% while 47.4% were found to have intermediate frailty. Three year mortality following PCI was 28% in frail compared to 6% in non-frail patients(67).Frailty measures capture the most prognostic information provided by the geriatric conditions after ACS(68). There are several risk calculators to predict short and long term outcomes after PCI and cardiac surgery as well. They were validated on a cohort of patients much younger and do not accurately identify older patients with higher risk. Current evidence suggest that further assessments are needed to risk assess patients of this high risk age group.

1.9 SURGICAL REVASCULARISATION IN THE OLDER PATIENTS

Cardiac bypass surgery among older population has been on the rise, however it is unclear whether the survival benefit is greater from PCI or CABG as the risk profiles differ between the patients selected for undergoing each intervention(23). Registry based evidence has an inherent selection bias against medically treated or PCI treated group as they are likely to include those turned down for cardiac surgery which can be a considerable proportion in the older population. The older patients who do undergo CABG surgery are a pre-selected group and hence the mortality data from this group cannot be extrapolated to the age group in general. In everyday practice EUROSCORE is used to risk stratify patients undergoing cardiac surgery, however evidence suggest that EUROSCORE overestimates the mortality risk in older patient group(69). This means that a proportion of patients who may benefit from cardiac surgery might be turned down.

Cardiac surgery in the older patients has been steadily on the rise over the last three decades. Evidence suggest open heart surgery to be a safer and effective option in older patients due to continual improvement in myocardial protection, surgical techniques, extracorporeal perfusion, anaesthetic protocols and post-operative care(70, 71). They remain a high risk group with multiple co-morbidities but acceptable post-operative mortality and morbidity. Mortality in octogenarians after bypass surgery has been reported to range between 6% to 24%(72-74). Off the pump CABG has been shown to be less invasive surgery with relatively reduced mortality, post-operative complications and recovery period (75, 76). Usually EUROSCORE and STS scores are utilised to predict postoperative mortality after cardiac surgery, however these risk scores have been validated in a much younger population and overestimates the operative risk in octogenarians and older patients(44). Furthermore it is unclear whether these patients derive greater survival benefit from PCI or CABG as the peri- procedural risk profiles differ between the group undergoing each intervention(23). The older patients who undergo CABG surgery are a highly selected group and the outcome data cannot be generalised to the whole age group. Cardiac surgery in this older adult group is associated with a prolonged recovery and higher incidence of discharge to nursing home compared to younger population(23). Whether hybrid revascularisation with minimally invasive approach offer a better option in this population remains to be determined.

1.10 PATIENT PREFERENCE AND PERSPECTIVE

Treatment that affords no benefit exposes the older patients to risk. The quality of life outcomes in older patients with ACS and after intervention are not well documented. The mortality and prognostic benefit in this population is usually off-set by their limited lifespan. In such a scenario the basic principles like respect for patient's preference and acting in patient's best interest apply. Besides making the patient and in some cases their families aware of the mortality and complication risk there should be discussion around possible loss of independency, prolonged hospitals stays and discharge to institutional care(9).

1.11 CONCLUSION

1. The number of older adult patients undergoing PCI has been on the rise.
2. They are usually a high risk group with higher post procedural mortality and morbidity.

3. Coronary artery disease tend to be more advance and complex in older patients and revascularisation in this age group poses a challenge to interventionists and surgeons alike.
4. Present risk assessment models were constructed on evidence from a much younger patient data and may not apply to older population with a different risk profile.
5. There is lack of robust data regarding management of coronary artery disease in older population. More age specific evidence base is needed to validate the current management strategies. The quality of available data is low for octogenarians undergoing coronary revascularisation(23).

2 CHAPTER- FRAILTY AND ITS ASSESSMENT IN OLDER ADULT POPULATION WITH CARDIOVASCULAR DISEASE- CONSIDERATION OF CLINICAL, ANATOMIC AND PATIENT FACTORS.

2.1 INTRODUCTION:

We have established in the first chapter that prevalence of cardiovascular disease in the older population is on the rise and the management strategies and risk assessments need to be individualised according to each patient's health. Older adult patients tend to have advance disease processes and a number of co-morbid conditions causing a considerable proportion of this population to become frail. Frailty is a geriatric syndrome encompassing impaired resistance to stressors due to a decline in physiological reserve of the body(77).Cardiovascular disease and frailty are both prevalent in the older population and often co-exist. Morbidity and mortality from CAD is strongly associated with both age and frailty(78). The disability free life expectancy in UK is around 65.5 years(2). In the following section, the concept of frailty and various frailty assessment tools will be described along with current evidence regarding its impact on patients with cardiovascular disease.

2.2 PREVALENCE OF FRAILTY IN OLDER ADULTS WITH CVD:

The prevalence of frailty varies in the scientific literature, depending upon the population being studied and the criteria used. In community setting, the prevalence of frailty is around 10.7% in the older population in general. This prevalence increases with age and is more in older women than men (9.6% vs 5.2%)(79).

2.2.1 COMMUNITY BASED PREVALENCE.

There is coexistence of frailty and cardiovascular disease in older patients, as incidence of both increase with age. In patients with cardiovascular disease frailty is three times more common than in patients without heart disease(80).This association seems not only cross-sectional across the older community population but there is some evidence of a longitudinal relationship. In community based studies, a higher prevalence of cardiovascular disease has been noted in the frail population (62% vs 28%) (81). In observational studies of community dwelling older population in United States, frail older population had higher prevalence of cardiovascular disease and

patients with cardiovascular disease were more likely to develop frailty over 6 years of follow-up(82, 83).

2.2.2 PREVALENCE IN HOSPITAL BASED SETTING

In hospital settings there is only limited data on prevalence of frailty. Most of these studies quote prevalence of frailty in particular condition or patients undergoing particular procedure rather than all comers. In patients more than 70 years of age with severe multi-vessel coronary artery disease the prevalence of frailty was around 27% to 50% depending upon the criteria used(84).This included only patients who underwent coronary catheterisation while frailty was assessed with either self-reported questionnaire or physical task based frailty assessment tools.

2.2.3 PREVALENCE IN PATIENTS CONSIDERED FOR CABG SURGERY.

Prevalence of frailty in older patients undergoing CABG surgery is high as most of them have advance underlying coronary artery disease. The reported prevalence has varied depending upon the criteria used to define frailty. Sundermann et al reported prevalence of 50% using a 35 criteria index while Afilalo et al showed 46% prevalence using gait speed criteria and concluded that frailty was strongly associated with poor outcomes (85, 86).

2.2.4 PREVALENCE IN PATIENTS CONSIDERED FOR TAVI SURGERY.

The patients referred for Trans-aortic valve intervention (TAVI) usually have advance age with multiple comorbid conditions and prevalence of frailty has been reported as high as 63%(87).In the Placement of Aortic Trans-catheter Valves (PARTNER) trial 48% of the participants were frail(88).

2.3 PROGNOSTIC VALUE OF FRAILTY IN OLDER ADULTS WITH CVD:

Frailty has prognostic value in patients with cardiovascular disease. Frail cardiovascular patients have been shown to have poor outcomes especially when faced with external stressors like surgery and interventions. A study of 628 patients who had successful PCI were assessed for frailty. There was significant difference in 3 year mortality between frail and non-frail patients (28% vs 6%). Presence of frailty in patient undergoing PCI increase the mortality risk 5 times and risk of MI about 2.5 folds(67).

In accordance with PCI data, frailty assessed by slow gait speed has been associated with a threefold rise in postoperative mortality or morbidity in patients undergoing

cardiac surgery. Slow gait speed has also been shown to increase the risk predictive value of Society of Thoracic Surgeons (STS) scores(89). Frail patients who undergo cardiac surgery not only have high post-operative mortality and morbidity but also have prolonged hospital stay and are less likely to be discharged to be discharged home(87). In patients treated with TAVR frailty predicted the need for institutional care due to functional decline and mortality at 1 year(88).

2.4 THE CONCEPT OF FRAILTY:

The concept of frailty has gradually evolved over the last two decades. Without any discrete parameters it has been assessed in a variety of ways. In 2013 a consensus report was developed for the first time to formulate an operational definition of frailty(90). The group defined frailty as

"A medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death."

Frailty is predominantly a geriatric syndrome. It needs to be differentiated from disability and co-morbidity which is also common in this age group and often co-exist with frailty. In the cardiovascular health study, Fried et al found 21.5% of the population was both frail , disable as well as had comorbidities(46). The domains which encompass this concept of frailty are outlined in the Table 2-1.

FRAILTY DOMIANS	INSTRUMENTS OF MEASURE
Nutritional Status	• Body Weight • Appetite • Body Mass Index (BMI)
Physical Activity	• Level of physical activity • Leisure time physical activity
Mobility	• Difficulty or needing help walking around the house • Gait speed
Energy Level	• Tiredness/fatigue • Low energy level/exhaustion
Strength	• Lifting an object that weighs over 5 kg
Cognition	• Memory problem • Diagnosed dementia/cognitive impairment
Mood	• Depression/depressed mood • Sadness • Anxiety • Nervousness
Social Support	• Social resources (when help is needed can someone provide this?) • Emptiness/missing people around

Table 2-1 : Main Domains outlining Frailty and various instruments of their measure. Adapted from De Vries et al, Outcome instruments to measure frailty. Ageing research review journal.

2.5 SOME BASIC CONCEPTS:

The concept of comorbidity, disability and frailty are well defined in geriatric medicine and should be differentiated.

2.5.1 COMORBIDITY:

Comorbidity can be defined as presence of two or more medical conditions/disease in the same individual.

2.5.2 DISABILITY:

Disability can be defined as inability or difficulty in performing everyday activities which are necessary for independent living. These activities are important part of quality of life of the individual(91). Disability can both be physical and mental.

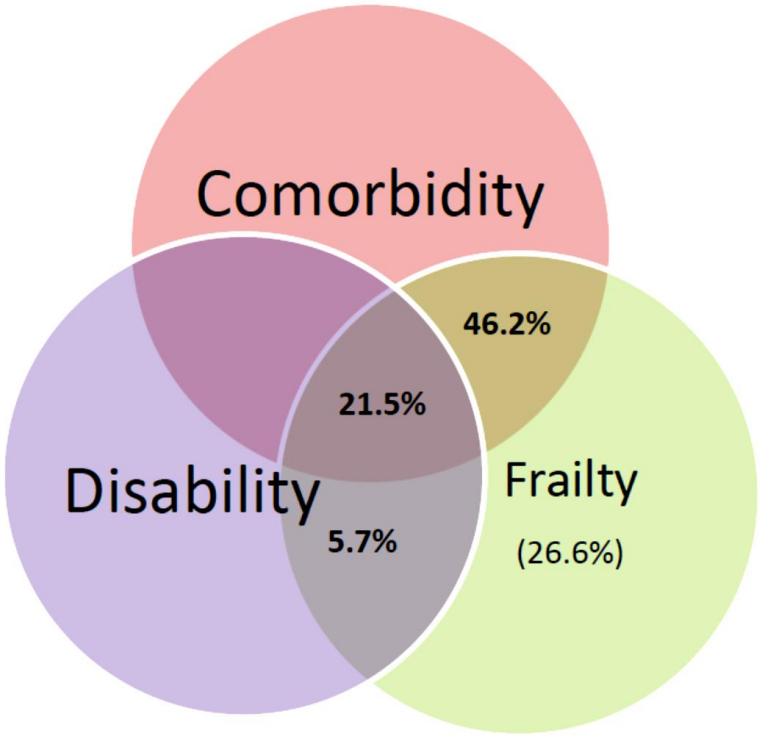


Figure 2-1: Venn diagram showing prevalence and overlap of comorbidity, disability and frailty in over 65 years population participating in cardiovascular health study (n=2762) (adapted from fried et al, Untangling concepts of disability, frailty and comorbidity. Journal of Gerontol A Boil Sci Med).

2.5.3 FRAILTY:

Frailty is a state of vulnerability which comprises of decline in body's ability to withstand major stressors as a result of reduced physiological reserves(91).

As can be interpreted from the definitions that these concepts are overlapping. Frailty can lead to disability and comorbidity and vice versa. Fried et al observed the overlap between these concepts (Figure 2-1).

2.6 PATHOPHYSIOLOGICAL MODELS FOR FRAILTY:

The underlying pathophysiology of frailty is still a topic of research and debate(92). Several mechanisms have been proposed and several questions have been answered after careful research. Is frailty actually accelerated aging? Frailty is certainly an age related process and there are certainly of overlap between normal aging and frailty syndrome but the two are not synonymous. A gradual decrease of physiological reserves occur with age. In frailty this process is accelerated and the homeostatic

mechanisms start to fail especially when the body is exposed to a physiological stressor(47).

2.6.1 FRAILTY AND AGING:

Both aging and frailty are characterised by multisystem dysregulation of the physiological mechanisms causing decreased physiological reserves leading to increase vulnerability to stressors. Hence both are similar in the sense that there is loss of body's physiological homeostasis. In the normal aging process this down regulation seems to be global while in frailty this seems to affect the energy metabolism and neuromuscular changes more(92). This suggests frailty to be a different process then aging and can be reversible unlike aging.

Furthermore the activation of the biomarkers is also different in frailty then the normal aging process(93). These include

i. Elevated cytokines and chemokines, Elevated interleukin 6 (IL-6) Levels.
ii. Reduced insulin like growth factor 1 (IGF-1)
iii. Relation with low endogenous steroids like dehydroepiandrosterone sulphate and leptins
iv. Elevated neutrophil and monocyte count(94).
v. Mild activation of coagulation system.

One feature of frailty that distinguishes it from aging is the potential reversibility of several features. Dietary and exercise intervention have been shown to reverse sarcopenia in frail people.

2.6.2 FRAILTY AND CO-MORBID CONDITION:

Is it possible that that frailty is the result of the co-morbidity burden? Evidence seems to be against this. When patients with major co-morbidities have been excluded from frailty studies, the difference in mortality between frail and non-frail population persists(93). It is unlikely that frailty is an outcome of chronic co-morbid disease. There is suggestion of a disease-independent inflammatory mechanism for frailty. The argument against this suggestion that this immune activation may be due subclinical disease processes that the patient might have especially subclinical cardiovascular disease. Co-morbid conditions especially cardiovascular diseases are seen as a risk factor for developing frailty.

2.6.3 THE PATHOGENESIS OF FRAILTY:

There are three principal pathophysiological elements which constitute the frailty model(95):

i. Sarcopenia (Low muscle mass)
ii. Immune dysfunction
iii. Neuroendocrine dysregulation

2.6.4 SARCOPENIA:

Body mass decreases incrementally after the age of 35 years. This decline may be masked by deposition of adipose tissue as the body weight usually continues to increase during the middle age. In old age especially over 75 year of age there is a decline in weight with loss of both lean body mass and the adipose tissue. This loss is characterised by loss of anabolic steroids like growth hormone, oestrogen and androgens. This process seems to be more marked in frail people. A decrease in muscle mass can lead to functional disability(95).

2.6.5 IMMUNE DYSREGULATION:

There is evidence of chronic immune activation in patients with frailty. This is where there seems to be a difference between frailty pathophysiological model and the normal aging process. In normal aging process there is reduction in stem cells leading to changes in T lymphocyte production and blunting of the antibody response to infections. Evidence suggest a persistent low grade inflammatory response in frailty that is hyper-responsive to stimuli and persist for a longer duration even when the stimulus is removed. Several cytokines markers of inflammation have been linked to frailty. They include interleukin-6, C reactive protein, Tissue necrotic factor-α (TNF-α) and CXC chemokine ligand-10(47). Another suggested model is of increased advance glycation end products which are produced by glycation of a variety of molecules at cellular level including proteins, lipids and nucleic acid. The production of these end products is up regulated by inflammation and cause cellular damage. These products have been linked to decline that occurs with aging and may have an important role in frailty as well. Another hypothesis is that that the low grade chronic inflammation may be a response to increasing burden of subclinical diseases in this population especially cardiovascular disease before they manifest clinically.

2.6.6 NEUROENDOCRINE DYSREGULATION:

Neurocognitive decline is one of the domains defining frailty. Frail patient are predisposed to not only functional, but also cognitive decline when exposed to acute physiological stressor. Studies have shown an important association between decline in cognitive function and hippocampus function. This evidence comes from study of patients with dementia and Alzheimer's disease (96, 97). It is also a key component of stress response as it responds to raised glucocorticoids level that relays with hypothalamus through a negative feedback mechanism(47). This stress response via hypothalamus may play a part in cognitive decline noted in some older adults if not frail patients after acute illness or post-surgery.

Another postulated model for delirium in the presence of physiological stressors like acute illness is hyper-responsiveness of primed microglial cell of the brain with age. The microglial cells are the resident immune cell for the central nervous system and are activated in response to both local and systemic inflammation. Over the years, they get primed to a number of stimuli. It is postulated that hyper-responsiveness to small stimuli in old age may lead to neuronal death and delirium in acute physiological settings(47). Frailty has been associated with increased risk of delirium in hospital setting(98).

The neuroendocrine deregulation seen in frailty involves deregulation of the homeostatic hormones through the hypothalamic pituitary axis. They are responsible for regulating the metabolism of the body. The exact mechanism of this process in frailty is unclear and needs further investigation. These neuro-hormonal changes do have similarity to changes that occur with aging and it may be that the frailty model is similar to normal aging but this remains to be established. What's known is that

- The concentration of IGF-I (Insulin like growth factor- I) in frail people is considerably lower compared to non-frail subjects of the same age. This decrease is thought to be as a result of decreased production of growth hormone. IGF-I is made by the liver and belongs to a group of peptides responsible for enhancing the anabolic activity at a cellular level in the body. However, this is part of the frailty syndrome rather the causative mechanism as trials of IGF-I supplementation have not shown any reversal of frailty in older frail population(99).

- Similarly there is association between frailty and decreased levels of testosterone and dihydrepiandesterone sulphate (DHEA). Whether this is casual association of part of the frailty syndrome is unclear.
- Chronically raised cortisol levels have been linked to frailty. Chronically raised cortisol has been seen in conditions with increased catabolism and may be the mechanism leading to decreased muscle mass and weight loss associated with frailty(47).

- Severe Vitamin D deficiency has been shown to be associated with frailty(100). However, the exact causal mechanism is still a topic of debate.

2.7 MEASUREMENT OF FRAILTY:

More than 20 assessment tools have been proposed to assess frailty in the older population(101)(Table 2.2). Broadly, these can be divided into two categories: one set of instrument assess what the person can do either by performing physical tasks or answering relevant questions, while others have assessed frailty by accumulation of deficits or things a person can't do. There is no single gold standard tool to measure frailty. The majority of these frailty measurement tools have been designed to assess frailty in the community dwelling population. Not all the tools have been validated and only a few have been tested in an inpatient setting. The call for action consensus document proposed all older adults above 70 years of age to undergo frailty screening(90). In UK an electronic frailty Index (eFI) has been introduced to screen for frailty both in primary care and hospital settings(102). It is an electronic tool that can identify patients with potential frailty by taking into account their electronic records. It takes into account factors like comorbidities, polypharmacy and functional deficiencies like walking aid, hearing loss or visual loss to remotely assess frailty.

Frailty is a complex concept and needs a well-structured instrument for assessment. An ideal health measurement instrument will have "*excellent content validity, internal consistency, criterion validity, reproducibility, longitudinal validity, responsiveness, floor and ceiling effect and interpretability*"(103). The clinometric properties of theses frailty assessment tools have not been thoroughly validated. The two instruments that have been most extensively externally validated are the Fried frailty phenotype(46) and Frailty index by Mitniski et al(101).

Frailty Indices	Nutritional Status	Physical activity	Mobility	Energy Level	Strength	Cognition	Mood	Social Support
Speechley et al(104). (1991)		Y	Y		Y	Y		
Frailty Measure. Strawbridge et al(105). (1998)	Y	Y	Y		Y	Y		
Dayhoff et al(106). (1998)	Y	Y	Y			Y	Y	Y
Modified Physical Performance Test(107). (2000)		Y	Y		Y			
Fried Frailty Phenotype(46). (2001)	Y	Y	Y	Y	Y		Y	
Groningen Frailty Index(108). (2001)	Y	Y	Y			Y	Y	Y
Frailty Index(109).Mitnitski et al (2002)	Y	Y	Y	Y		Y	Y	Y
Binder et al(110). (2002)	Y	Y	Y	Y	Y	Y	Y	Y
Gill et al(111) (2002)			Y					
Klein Frailty index(112). (2003)			Y		Y			
Clinical Global Impression of change in Physical frailty –CGIC-PF(113). (2004)	Y	Y	Y	Y	Y	Y	Y	Y
EPIDOS Dependence Index(114). (2005)	Y	Y	Y		Y			
Clinical frailty scale(115) (2005)		Y	Y					
Static/Dynamic Frailty index(116). (2005)	Y	Y	Y	Y		Y	Y	
Frailty Staging System(117). (2005)		Y	Y			Y		Y
Edmonton Frailty scale(118). (2006)	Y	Y	Y	Y	Y	Y	Y	Y
Short Physical Performance Battery(119). (2006)			Y					
Margliano-Cacciafesta polypathological scale. (2008)		Y	Y			Y	Y	
Study of Osteoporotic fractures Index(120). (2008)	Y		Y	Y			Y	
HRCA Vulnerability Index(121). (2008)		Y	Y			Y		
Tilburg Frailty Index(122). (2010)	Y	Y	Y	Y	Y	Y	Y	Y
FRAIL scale(123). (2010)	Y	Y	Y	Y		Y	Y	Y
Brief Frailty Index(124). (2010)	Y	Y	Y				Y	Y
Opasich et al(125). (2010)		Y	Y					
Comprehensive Assessment of Frailty(85). (2011)	Y	Y	Y	Y	Y		Y	
SHARE-FI(126). (2010)	Y	Y	Y	Y	Y			
Gerontopole Frailty Screening Tool. (2012)	Y	Y	Y	Y		Y		Y

Table 2-2: Various Frailty Indices used in different clinical trials over the years and the frailty domains measured by them.

2.8 BIOMARKERS OF FRAILTY:

Both aging and frailty are characterised by multisystem dysregulation of the physiological mechanisms leading to decrease physiological reserves increasing vulnerability to stressors. In the normal aging process this down regulation seems to be global while in frailty these seem to affect the energy metabolism and neuromuscular changes more(92). So far there is no blood test to diagnose or monitor frailty. The changes in biochemical markers observed in frail patients are listed in table 2-3.

Biological markers noted to Increase in frail patients	**Biological markers noted to decrease in frail population**
CRP (Immune activation)(93)	Transthyretin (visceral protein depletion)
Factor VIII (Coagulation activation)(93)	Retinol binding protein (visceral protein depletion)
Fibrinogen(Acute phase reactant)(93)	Albumin
IL-6 (Immune activation)(93, 127, 128)	Growth hormone,
D dimer (Coagulation activation)	IGF-1(127)
Factor Xia	Vitamin D(129)
Alpha 1 antitrypsin level	Dehydroepiandrosterone sulphate(127)
24 hr mean cortisol	Lipopolysaccharide induced peripheral blood mononuclear cells(128, 130)
CD8+CD28(131)	

Table 2-3: Variation in biochemical markers observed in frail patients.

2.9 ASSESSMENT OF FRAILTY IN CLINICAL PRACTICE:

Given the added prognostic value frailty assessment has to offer, it is recommended for older cardiovascular patients undergoing high-risk procedures or surgery. Frailty should not be a reason to withhold care but a tool to identify these high risk individuals in order to structure their care to optimise outcomes(87). Assessment of frailty in patients undergoing cardiac surgery has been shown to add incremental value to traditional risk scores in identifying older patients at high risk of mortality and morbidity(86). This is important in order to ensure appropriate information is provided to patients when consenting to procedures. In addition, it raises the possibility that once frailty has been identified, patients could receive an intervention in order to improve frailty status and thereby reduce the surgical risk. This might encompass a prescribed exercise programme as pre-habilitation which can be tailored to cover all the areas of frailty(132, 133) as well as nutritional support. A brief synopsis of the current evidence base of frailty assessment used in patients with

cardiovascular disease is given in Table 2-4. Table 2-5 briefly covers studies of frailty in heart failure, cardiac surgery and TAVI patients.

Table 2-4 : Evidence Base for impact of frailty on patients with cardiovascular diseases.

Study/Authors	Year of Study	Number of Patients	Age	Study design and objective	Frailty model used	Prevalence of frailty	Results
CARDIOVASCULAR DISEASE (CVD)							
Sergi et al(134)	2015	1567	73.6±6.7	Prospective observational cohort study. To ascertain whether pre-frailty can predict onset of cardiovascular disease	Modified Fried criteria		Pre-frailty was independently associated with higher risk of developing cardiovascular disease in older adults. Slow gait speed was the best predictor of future cardiovascular disease.
Singh et al(135)	2012	3571	N/A	Prospective multicentre cohort study, To assess relationship between frailty and subclinical cardiovascular disease with focus on peripheral vascular disease	Modified Fried Scale	18%	Cardiovascular mortality was 29% vs 6%
Klein et al(136)	2005	2962		Community based cohort. Prospective observational study. To investigated association of frailty to disease outcomes.	Index made of gait time, handgrip strength, peak respiratory flow rate, standing from sitting position, visual acuity		Greater frailty was associated with CVD
Newmann et al(137)	2000	4735	77.2	Community dwelling cohort. To determine association of frailty and cardiovascular disease	Modified Fried Criteria	6% were Frail and 45% had intermediate frailty	Frailty status was associated with clinical CVD and most strongly with heart failure. In patients without any h/o of CVD non-invasive measures of CVD related to frailty

Study/Authors	Year of Study	Number of Patients	Age	Study design and objective	Frailty model used	Prevalence of frailty	Results
ACS/INTERVENTIONAL STUDIES							
Krishnan et al(48)	2015	745	62±12	Prospective cohort study. Relationship between frailty and PCI outcomes	Clinical frailty scale(CSHA-FS)	11% (81)	Frail patients required longer hospitalisation after PCI. Frailty was also associated with increased 30-day (HR 4.8, 95% CI 1.4 to 16.3, p=0.013) and 1 year mortality (HR 5.9, 95% CI 2.5 to 13.8, p<0.001). Frailty was a predictor of length of hospital stay and mortality, independent of age, gender and comorbidities.
Salinas et al(138)	2015	202	83.8±5.7	To assess prevalence of frailty and its impact on inpatient adverse outcomes	SHARE-FI Index	35.1%	Frailty phenotype is an independent prognostic marker in these patients. Frail patients had high all-cause mortality (8.5 vs 0.8%)
Ekerstad et al(139)	2014	307	75 and above	Prospective, multicenter, Patients with NSTEMI. To determine association of frailty with outcomes at 1 yr.	CSHA Clinical frailty scale	48.5%	Frailty was independently associated with 1 year mortality.
Graham et al(140)	2013	183	75.3	To assess impact of frailty on older patients with ACS	Edmonton frailty scale		Higher frailty scores were associated with high incidence of HF, higher mortality, longer hospital stay and decreased procedural use.
FATE-ACS Study(141)	2013	629	68±10	Prospective, hospital based, To assess predictive power of simple frailty score in	Gold standard framework (GSF) score	8.3%	GSF used in hospital setting identifies considerable proportion of patients at high risk of death at 12 months.

Study/Authors	Year of Study	Number of Patients	Age	Study design and objective	Frailty model used	Prevalence of frailty	Results
				identifying ACS patients approaching end of life.			
Matsuzawa et al(142)	2013	472	63.1±11.8	Prospective, observational, To determine additional clinical value of gait speed in addition to Framingham risk score in predicting cardiovascular events in STEMI patients	Gait Speed	67.2%	In STEMI patients slow gait speed was significantly associated with increased risk of future cardiovascular events.
Gharacholou et al(143)	2012	545	>65	Prospective, To assess prevalence of frailty and its association with health status in PCI treated patients.	Fried criteria	19% (117)	1/5 of older patients are frail at time of PCI and have greater comorbidity burden, angiographic disease severity and poor health status than non-frail patients.
Singh et al(67)	2011	628	77±6.8	Prospective observational, to assess influence of frailty on outcomes in patients undergoing percutaneous revascularisation	Fried Criteria	18%	Following PCI frailty, comorbidity and poor QoL is prevalent and associated with adverse outcomes. Three year mortality 28% in frail vs 6% in nonfrail.

Table 2-5: Synopsis of studies investigating frailty in heart failure, cardiac surgery and transcutaneous aortic valve intervention (TAVI) patients

Study/Authors	Year of Study	Number of Patients	Age	Study design and objective	Frailty model used	Prevalence of frailty	Results
HEART FAILURE STUDIES							
McNallan et al(144)	2013	448	73±13	Prospective, observational, To determine prevalence of frailty in HF patient cohort	Modified Fried criteria	19% Frail, 55% intermediate frail.	Frailty was associated with 92% increased risk of ED visits and 65% increased risk of hospitalisation.
Polidoro et al(145)	2013	140	79.2±7.4	Hospitalised patients, control group. To investigate association of frailty, AF and cognitive decline	Frailty Index	88.6% in hospitalised AF patients	Higher prevalence of frailty in AF patients and had significantly lower MMSE than control group.
Khan et al(146)	2013	2825	74±3	To assess relationship between frailty and heart failure	Health ABC Short Physical Performance Battery (HABC Battery)	50.4%	Frailty is independently associated with heart failure in older adults
Lupon et al(147)	2008	622 (344 were >70)	68	To assess impact of frailty on one year mortality rate and hospitalisation in patients with heart failure	Frailty assesses by several instruments like Barthel Index, OARS scale, The Pfeiffer Test, geriatric depression scale	52.5%	Significant relationship between frailty and one year mortality (16.9% vs 4.8%) in heart failure patients.

Study/Authors	Year of Study	Number of Patients	Age	Study design and objective	Frailty model used	Prevalence of frailty	Results
Cacciatore et al(117)	2005	120	75.9±6.7	To examine predictive role of frailty in long tern mortality in older patients with HF	Frailty Staging System	15%	Frailty in more predictive of long term mortality in older patients with HF than in those without HF.
CARDIAC SURGERY STUDIES							
Sundermann et al(148)	2011	213	80.1±4	Prospective, observational, assessment of perioperative risk of older patients undergoing cardiac surgery.	Comprehensive assessment of frailty (CAF), FORECAST	53.5% in patient undergoing surgery	Frailty predicts death at one year after cardiac surgery
Lee et al(149)	2010	3826	71 frail, 66 non frail,	Prospective, observational, to determine impact of frailty on mortality and post-operative institutional care	Any impairment in activity of daily living(Katz Index), ambulation or h/o dementia	4.1%	Frailty is a risk for postoperative complications and an independent predictor for in-hospital mortality, institutional discharge and reduced mid-term survival
Afilalo et al(89) Frailty ABCs	2010	131	75.8±4.4	Multicentre, prospective, observational, To test the value of gait speed as predictor of postoperative mortality and morbidity	Gait speed	46%	Slow gait speed was an independent predictor of mortality and major morbidity.
TAVI STUDIES							
Yamamoto et al(150)	2015	777	85±6.7	Multicentre retrospective registry based. To study impact of low BMI on clinical outcomes after TAVI	BMI less than 20 was taken as indicator of frailty	7.2%	BMI less than 20 was not associated with increase early or midterm mortality.
Osnabrugge et al(151)	2015	436	84±8.5	Multicentre, prospective, observational study, To	Kansas City Cardiomyopath	65.7-84.5%	Substantial improvement in quality of life after TAVI was seen with a large

Study/Authors	Year of Study	Number of Patients	Age	Study design and objective	Frailty model used	Prevalence of frailty	Results
				assess quality of life in patients undergoing TAVI and identify characteristics associated with poor outcome	y Questionnaire (KCCQ), 5 meter gait speed, 6 minute walk, grip strength, Katz activities of daily living		minority with high mortality and QoL despite TAVI. Frailty may provide insight into optimal patient population for TAVI.
Puls et al(152)	2014	300	82±5	Single centre prospective. To assess impact of frailty on short and long-term mortality after TAVI	Katz index<6 was taken as frail	48%	Frailty status measured by Katz status represented a powerful predictor of adverse early and late outcomes.
Green et al(88)	2012	159	86±8	Hospital based cohort, prospective, To determine impact of frailty on older adults undergoing TAVI	Gait speed, grip strength, serum albumin, activities of daily living	47.7%	Frailty was not associated with high peri-procedural complications but increased mortality at 1 year after TAVI
Cabau et al(153)	2012	339	81±8	Hospital based cohort, prospective, observational, Main aim of study was to see long term outcomes of TAVI	Bedside clinical impression	25.1%	Frailty was associated independently with long term outcomes after TAVI.
Schoenenberger et al(154)	2012	119	83.4±4.6	Prospective, observational, To assess predictors of functional decline after TAVI	Mini-mental state, mini nutritional assessment, Basic activities of daily living (BADL), Instrumental	49.5%	Over 6 month follow up Frailty Index and not conventional risk scores was predictive of functional decline.

Study/Authors	Year of Study	Number of Patients	Age	Study design and objective	Frailty model used	Prevalence of frailty	Results
					activities of daily living (IADL)		

2.10 FRAILTY INTERVENTION IN CARDIOVASCULAR PATIENTS

Frailty in early stages is potentially reversible. Assessment of various frailty domains can help tailor specific intervention to reduce frailty. The 2013 frailty consensus statement recognised four possible treatments to treat frailty.

1. Exercise prescription as prehabilitation
2. Nutritional Support
3. Vitamin D supplement
4. Polypharmacy control

Exercise prescription improves outcomes of patients with ischaemic heart disease and is usually underutilised despite evidence of improving outcomes(155), but rehabilitation is done after the physiological stressor has passed. It may be particularly beneficial for frail patients in targeting their area of deficits even before they are exposed to the anticipated physiological stressor as surgery. This has led to development of concept of prehabiltation. To improve outcomes protocols may need to be modified for frail patients. However, the problem with cardiovascular patients especially with coronary artery disease is that they present acutely and need to be treated promptly, hence not leaving any margin for prehabilitation. The role of prehabilitation in frail patients to improve their outcomes after surgery is a rich area for research. These programs can also be used to monitor their progress(156). Nutritional supplements and increased dietary proteins have been advised to increase muscle mass and improve grip strength along with resistance exercise in frail older patients(157, 158). Vitamin D supplement and low frequency exercise has been shown to reduce falls in frail older patients(159). Meta-analyses done by Bolland et al suggest a modest increased risk of MI with calcium supplementation with and without vitamin D and advised further research(160). Evidence regarding interventions for targeting frailty in cardiovascular patients is limited and further research is needed in this area.

2.11 CONCLUSION:

1) Frailty is characterised by reduced muscle strength, endurance and reduced physiological reserve which increases the individual's vulnerability when faced with physiological stressors as acute disease or surgery.

2) Frailty has been conceptualised by various domains like physical activity, mobility, nutritional status, energy level, strength, cognition, mood and social support. There are numerous frailty assessment measures which can be used.
3) In older population there is a considerable overlap between comorbidity, disability and frailty.
4) There is increased prevalence of frailty in older adult patients with cardiovascular disease which carries adverse prognostic implications.
5) There is scarcity of evidence exploring frailty in very old octogenarian patients presenting with symptomatic coronary artery disease.

3 CHAPTER- RATIONALE BEHIND RESEARCH PROJECT-QUESTIONS AND STUDY DESIGN

Having gone through the available literature and evidence in detail, we set the rationale behind this research project. The main research philosophy behind this study was to explore what happens to these older individuals when they present to hospital, with symptoms of coronary artery disease. The main research questions we wanted to answer were as follow,

3.1.1 RESEARCH QUESTION 1:

WHAT ARE THE CLINICAL AND PHYSICAL CHARACTERISTICS INCLUDING FRAILTY AND HEALTH RELATED QUALITY OF LIFE OF THIS GROUP OF OLDER ADULT PATIENTS BEING TREATED FOR CORONARY ARTERY DISEASE?

The health characteristics vary considerably in older population. For our study purpose older adults refer to elderly above eighty years of age. We wanted to know in detail about this select group of patients. To better define their physical and clinical characteristics, we decided to gather extensive number of variables about the study participants to get a clearer picture of their health. Frailty is quite prevalent in this age group. We assessed their frailty status and recorded their health related quality of life.

3.1.2 RESEARCH QUESTION 2:

WHAT FACTORS INFLUENCES THE QUALITY OF LIFE OF OLDER PATIENTS PRESENTING WITH CORONARY ARTERY DISEASE AND EFFECT OF VARIOUS MANAGEMENT STRATEGIES INCLUDING MEDICAL THERAPY, PERCUTANEOUS INTERVENTION AND BYPASS SURGERY HAVE ON THEIR QUALITY OF LIFE?

Evidence suggest that improvement in quality of life may be more relevant outcome in these older patients undergoing various treatment for their coronary artery disease. We designed an observational study model to explore how these management strategies effect their quality of life.

3.1.3 RESEARCH QUESTION 3:

DOES VARIOUS MANAGEMENT STRATEGIES FOR ACUTE CORONARY DISEASE IMPROVE THE QUALITY OF LIFE AND FRAILTY STATUS OF OLDER OCTOGENARIANS WITH SYMPTOMATIC CORONARY ARTERY DISEASE?

Having established that increasing number of octogenarians are undergoing percutaneous intervention procedures and cardiac bypass surgery than before, we

wanted to see what sort of benefit they derived undergoing these intervention. Most of these patients are likely living the last decade of their life and the mortality benefit of these management strategies is usually offset by their reduced life span. As already pointed out in introductory chapters, the evidence base of treatments for this age group is derived from studies done on a much younger population and the same may not apply to these patients. We decided to move away from measuring reduction in mortality or MACE (Major adverse clinical event) as the primary outcome. Rather we wanted to measure an improvement in health related quality of life as the primary outcome as it is more relevant in this population of octogenarians living last decade of their life.

3.2 NULL HYPOTHESIS.

The null hypothesis behind our study is that 'Frailty is not related to health related quality of life in this octogenarian cohort of patients presenting with symptomatic coronary artery disease'.

3.3 RATIONALE BEHIND STUDY DESIGN.

Having these questions in our mind we designed our study. As we were not just testing a single hypothesis, but trying to get a clearer picture of how our older study cohort with coronary artery disease faired through their treatments, we designed a prospective observational study rather than a cross-sectional one. We wanted a holistic picture of what was happening to these patients, so we decided to recruit non-selected and consecutive patients across the whole spectrum of coronary artery disease including stable angina as well as acute coronary syndromes. Hence the participants were recruited after exposure to their disease, but their condition was assessed after recruitment into the study in a temporal manner. We aimed to design the study in way that we could assess frailty status and quality of life of the participants before they underwent their respective treatments and then reassess them after 3months of undergoing their treatments. The study design has been described in detail in the next chapter.

The literature review suggested a number of frailty assessment tools available. We selected Fried frailty scale because it was the most cited frailty scale and has been used extensively in scientific research. We selected Edmonton frailty scale as it covered all the frailty domains. It assessed cognitive function in details with a "Draw a clock- face test" and also documented independent activity of daily living (IADL) as part of the scale.

We selected SF-12 short survey form to assess the health related quality of life parameters for the study. SF-12 is a short form of extensively utilised SF-36 form, which is one of the most validated QoL questionnaire used in clinical research. SF-12 survey form has lesser question burden with comparable sensitivity and specificity to SF-36 form. As our study assessment involved completing a number of questionnaire we decided to use SF-12 form to reduce participant's burden.

We aimed to follow up at 3 months after the participants had undergone their treatments. This was done after some deliberation. We wanted to assess the impact of their treatments on their quality of life and frailty. Three months was thought to be enough for the participants to recover from their illness, procedures or surgery. However, due to logistic constraints the actual mean follow up period for the study participants was around 114 days (4 months). The study cohort comprised to older adult patients with a number of co-morbid conditions at times. A longer follow up time would increase their chance of becoming unwell due to other illnesses.

4 CHAPTER- RESEARCH DESIGN AND METHODS OF FRAIL-HEART STUDY.

4.1 RESEARCH DESIGN:

To evaluate the real life relationship between 'frailty' and 'quality of life' in older individuals over 80 years of age a prospective observational study model was proposed. We included unselected older adult patients presenting with symptomatic coronary artery disease. Patients aged 80 years or over and who attended Castle Hill Hospital with any spectrum of coronary artery disease like stable angina or an acute coronary syndrome were invited to participate in the study. After induction into the study, these patients were assessed for frailty and quality of life (QoL) using predetermined assessment tools. Quality of life (QoL) was assessed using the standardised SF-12 questionnaire Performa. Frailty assessment was based on the use of the Fried Frailty Phenotype criteria and the Edmonton Frailty Scale(46, 118) Patients were reassessed at 4 months after their treatments for clinical outcomes, repeat frailty assessment and quality of life.

4.2 SCOPE OF THE STUDY

4.2.1 WHAT IS ALREADY KNOWN ABOUT THE SUBJECT?

The evidence base on the topic has been extensively covered in the initial chapters of the thesis.

4.2.2 WHAT WILL THIS STUDY ADD?

1. FRAIL-HEART study specifically focuses on older adult group of octogenarians and will add to the scarce evidence base available about these patients likely leading the last decade of their life.

2. This study will not only add to the evidence of frailty assessment in patients undergoing percutaneous intervention but also give a holistic picture of older adults with symptoms across the whole spectrum of coronary artery disease. Although there a number of studies assessing frailty in patients undergoing cardiothoracic surgery, trans-catheter aortic valve replacement but only a few assessing its impact in patients undergoing percutaneous coronary intervention and most of them are based on retrospective registry data .

3. The prognostic benefit of cardiovascular intervention in this older age group is offset by their limited life span. The FRAIL-HEART study will assess the

association of frailty and quality of life in this select group. There is very limited evidence on this subject. FRAIL-HEART will be among a few studies using the QoL short survey form SF-12.

4. FRAIL-HEART study will be among a few studies evaluating impact of frailty on quality of life in older adults who have been managed medically for their CAD. There are a few studies assessing mortality and morbidity in medically managed patients but none assessing QoL.

4.2.3 HOW THIS MIGHT IMPACT ON CLINICAL PRACTICE?

This study will help to provide information about the influence of frailty in an unselected population of older patients with CAD. The results will help to understand the importance of frailty on QOL and will enable further large-scale studies to be designed and undertaken. The results will help better inform older adult patients and their families, particularly those being considered for revascularisation as it may help us identify patients who are at high risk from these procedures and treatments. If this study can demonstrate utility in undertaking frailty assessments then in the future, this information can be routinely incorporated into discussions about optimal patient management.

4.3 STUDY GOALS AND OBJECTIVES:

4.3.1 PRIMARY OBJECTIVE:

The primary aim of this study was to evaluate the relationship between frailty and quality of life (QoL) at baseline and short term follow-up.

4.3.2 SECONDARY OBJECTIVES:

Secondary objectives were as follow:

1. To evaluate change in frailty at baseline and 4 month follow-up using the Fried frailty criteria and the Edmonton frailty score.

2. To explore the change in QoL using the standardised SF-12 with respect to the treatment received (medical therapy, PCI or CABG).

3. To evaluate the occurrence of major adverse clinical events (defined as a composite of death, heart attack, acute stroke, and major bleeding) in frail versus non-frail participants of the study.

4. To identify which patient factors were associated with an increased risk of an adverse outcome (defined as death or a worsening in QoL).

5. To explore the relationship between Vitamin D levels and frailty in this older adult group of patients with CAD.

4.4 STUDY POPULATION:

4.4.1 INCLUSION CRITERIA:

All patients included in the study fulfilled the following criteria:

Patient aged 80 years and above and either,

a. Had been seen in the cardiology out-patient department with a diagnosis of stable angina

b. Had been admitted to Castle Hill Hospital with non-ST elevation acute myocardial infarction (NSTEMI)

c. Had been admitted to Castle Hill Hospital with ST-elevation acute myocardial infarction (STEMI)

d. Had been referred to Castle Hill Hospital for coronary angioplasty

e. Had been referred to Castle Hill Hospital for coronary artery bypass graft surgery.

4.4.2 EXCLUSION CRITERIA:

Patients were excluded from the study in the event of any of the following:

a. Patients who were unable to provide informed consent including those with advanced dementia and memory problems.

b. Patients with established diagnosis of heart failure based on presence of left ventricle dysfunction on their last echocardiogram.

c. Patients, who were not able to speak good English sufficiently to be able to understand the study information, give consent and complete study measures and questionnaires.

d. Patients who had a primary diagnosis of significant valvular disease

4.5 SAMPLE SIZE CALCULATION:

This was a preliminary observational study, designed to evaluate the practicality of undertaking frailty assessments in this population. The sample size of n=150 was estimated on the basis of feasibility. We aimed to recruit consecutive patients who attend our department over a 1 year period. In 2014, the department saw 283 patients aged 80 years or more who underwent coronary angiography +/- angioplasty, plus an additional 27 patients who underwent CABG surgery. There were also more than 50 patients who were seen in the out-patient clinic and were subsequently managed on medical therapy alone. This equated to 360 patients over a year which made recruitment of 150 patients an achievable target.

The department had been undertaking a study in patients with heart failure that incorporated a frailty assessment (OPERA-HF) and therefore provided some indication of the likely enrolment rate. A total of more than 500 patients had been recruited for the study. Successful enrolment was achieved in 64% of patients screened for the study. On the basis of this figure, we anticipate that we will be able to recruit 230 out of the potential 360 patients. With an anticipated drop-out rate of 10% we estimated that it would be feasible to enrol 150 patients in the required time-frame.

4.6 IDENTIFICATION AND RECRUITMENT PROCESS:

These patients were recruited into the study from outpatient cardiology clinics and from inpatients admitted to the cardiology and cardiothoracic units. The initial approach to participate in the study was in most cases made by the members of the clinical or cardiology team looking after the patients. They were given an invitation brochure and individuals who were willing to consider study participation were given the study patient information leaflet and the clinician sought permission to pass their details on to a member of the research team.

If the patient was agreeable, the member of the research team explained in detail what the study would involve and what would be expected from them. They were given the opportunity to think, discuss with family and friends and ask questions before consenting. In general they had at least 24 hours between receiving the patient information leaflet and consent, but as this is an observational study only, with limited participant burden, if a patient was keen to consent before, then this was allowed. This also ensured that in some circumstances, e.g. a patient who was due to be discharged home later that same day; will not have the additional burden of a repeat trip to hospital to complete the baseline measures.

All participants were reassured that they could withdraw at any time without having to give a reason, and without affecting their clinical care. Once the participants had provided consent they were allocated a specific study ID number.

4.7 DATA COLLECTION:

4.7.1 BASELINE ASSESSMENT:

The baseline assessment included gathering patient baseline demographic data, current diagnosis and clinical status, assessment of the comorbid conditions via Charlson score. Information regarding relevant investigation results including blood results, electrocardiogram (ECG), echocardiogram and coronary angiography data was also recorded. The patient's clinical data was also used to calculate GRACE score which included age, heart rate, systolic blood pressure, serum creatinine level, congestive heart failure, cardiac arrest at admission, ST-deviation on ECG and elevated cardiac enzymes(12). NYHA classification was used to assess participant's shortness of breath and functional capacity. Similarly CCS angina classification was used to assess chest pan symptoms of patients. Patients who presented with STEMI were graded as CCS class 4.This was done to reflect their symptom burden. The patients presenting with STEMI were only group recruited after they had undergone their treatments, hence when assessing their quality of life and frailty they were asked to reflect on their health status prior to admission. Their baseline assessments were carried out after they had been cleared by cardiac rehabilitation and physiotherapist to go home. The symptoms were graded again at follow up according to same classification: NYHA (New York Heart Association) classification for shortness of breath, CCS (Canadian Cardiovascular Society) classification for chest pain and KILLIP classification for post MI heart failure(161). If patients did not have routine blood samples taken recently then they were performed to include FBC, BCP, glucose, CRP, NT-proBNP, and Vitamin D. Patients were asked to complete QoL questionnaire and undergo the frailty assessments.

4.7.2 SF-12 QoL QUESTIONNAIRE(162) (APPENDIX 7):

Health related quality of life (QoL) was used as the primary outcome for analysis. There are a number of health related QoL questionnaires found in the scientific literature. SF-36 (Medical outcome study short form 36) is one of the well-known QoL assessment tools which has been extensively used and validated in the medical literature. SF-12 (Medical outcome study short survey form 12) (see Appendix 7) is a shorter form of SF-36(162), that has been shown to have comparable accuracy to the SF-36 but has the

major advantage that it can be completed in a much shorter time frame. This reduces respondent's burden which is important for older participants. Another advantage of using SF-12 form is its norm-based scoring system rather than aggregate scoring. The scoring software also compares the individual scores with those of normal Caucasian population in United states and Canada, matched for age and gender(163). For the purpose of the study, user licence was bought for the software which was installed on the university computers. Anonymised data was entered into the software to calculate the scores and no data was sent or shared out. SF-12 survey form has been validated against SF-36 in various settings (164). However for research purpose, specific tools might be needed depending on the research setting. In surgical patients where post surgery pain in a major factor affecting QoL specific pain sensitive tools may be more valid.

4.7.3 MEASURES OF FRAILTY:

Based on the published data regarding clinical validity, the Fried Frailty Phenotype and Edmonton Frailty Scale were the frailty assessment tools selected for this study.

4.7.3.1 FRIED FRAILTY PHENOTYPE:

Fried frailty phenotype was proposed by Fried et al back in 2001(46). It remains one of the most cited frailty assessment tool in literature(101). (See figure 4-1). It is the most validated frailty measure and at times has been used the "gold standard" by later frailty studies(24). It is a mixed frailty assessment tool and comprises of both questionnaires and physical performance tasks. It covers five frailty domains, namely

- Nutritional Status: assessed by unintentional weight loss of more than 10 pounds over the last year.
- Mood and energy level: assessed by documenting feeling of exhaustion and inability of getting on with life. The questions used were adapted from Centre of Epidemiological Studies (CES-D) depression scale(165).
- Physical activity: assessed by calculating the kcal (kilocalories) pent in a week with the help of modified short version of Minnesota Leisure Time Activity questionnaire(166).
- Mobility: assessed with the help of gait speed. Participants were asked to walk for 5 meters and time taken was recorded.
- Strength: assessed by recording the grip strength.

Details of the questionnaire used and their marking scheme are attached in appendix 3.

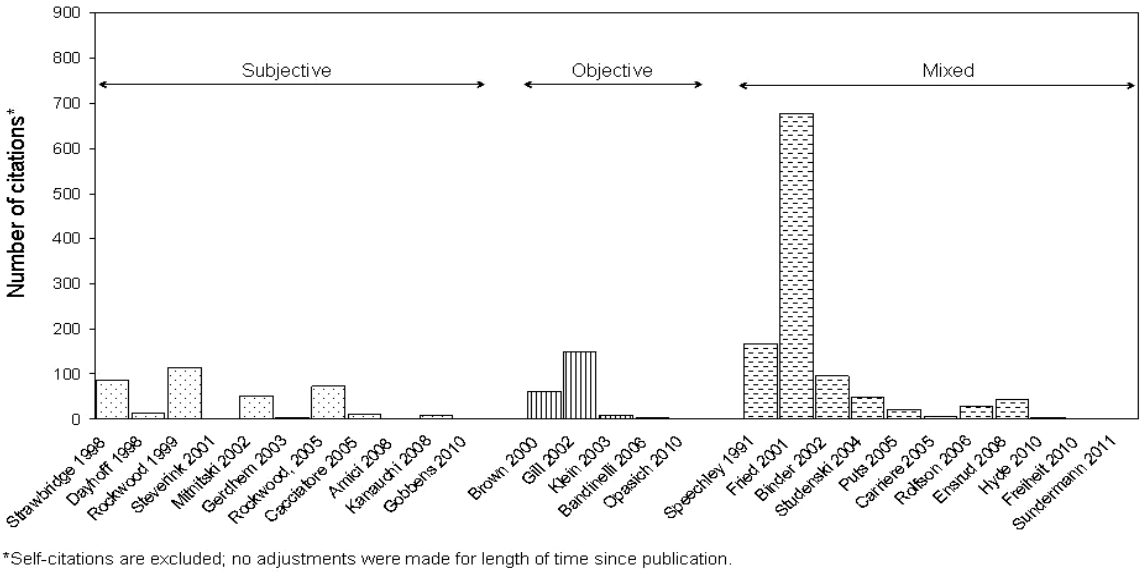


Figure 4-1: Citations referenced in Scopus database showing the number of times each frailty index has been cited. (Adapted from 'Measures of frailty in population-based studies: an overview')

4.7.3.2 EDMONTON FRAILTY SCORE:

Edmonton frailty scale was formulated by Rolfson et al in 2006(118) and has also been validated. The Edmonton frailty scale was selected for the present study because it covers all the main frailty domains, as well as neuro-cognition. Cognitive decline is an important component contributing to frailty in the older adult population. The domains included in Edmonton frailty score are as follow

- Cognition: assessed by asking the participant to draw a clock face and show a particular time.
- General Health Status: assessed by documenting the number of admissions participants had during the last year and also asking them how they graded their health in general.
- Functional Independence: assessed by asking whether participants needed help with specified everyday activities.
- Social Support: assessed by asking participants whether they had help available whenever they needed it.

- Medication use: Polypharmacy was documented by asking if participants were taking more than five different prescription medications. They were also asked if they forgot to take their medications.
- Nutrition: assessed by asking if the participants had lost any weight.
- Mood: assessed by directly asking them if they had been feeling sad or depressed.
- Continence: Participants were asked if they had any problem with urine continence.
- Functional performance: assessed with 'get up and go' test. Participants were asked to get up from a chair walk 3 meters and return to the chair. The time taken to complete the task was recorded.

Frailty was evaluated using both the Fried phenotype and Edmonton frailty scale (Appendix 2 and 3). Study participants were first asked to complete the written questionnaires. They then had a measure of handgrip strength and if feasible were asked to do 'get up and go' and 'five metre (16ft) walk 'test as detailed in the Edmonton and Fried assessments respectively. Participants who were unable to walk were marked as per the criteria. Participants were allowed to use walking aids if required.

Where applicable, the research team also evaluated the results of coronary angiography and undertook EUROSCORE(167) calculations in order to evaluate the preferred mode of revascularisation and the predicted risk. SYNTAX score(30) is an angiographic score that helps to assess the complexity of coronary artery disease. EUROSCORE is a risk score that estimates the risk of death after cardiac surgery.

Participants who were inpatient completed exactly the same assessments whilst in hospital once they are clinically stable. Mobility assessments were not attempted unless the patient was deemed by their treating clinical team to be fit enough to be mobile on the ward.

4.7.4 FOLLOW UP ASSESSMENTS:

The study participants were then seen at 4 months interval and were asked to complete the QoL questionnaire and undergo frailty assessment. The following variables were recorded at follow-up visit.

- Patient symptoms- CCS angina class, NYHA class
- Height, weight, BMI, Vital signs
- Medication with dosages
- All major adverse outcomes: myocardial infarction, acute cerebrovascular event, major bleeding, or unplanned re-hospitalisation.
- Any other adverse events such as kidney injury, transient ischaemic attack.
- Total length of hospital stay (where applicable).
- SF-12 questionnaire(162)
- Fried Frailty phenotype(46)
- Edmonton frailty scale(118)
- Patient perspective survey form (Appendix-5)- Two separate patient's perspective survey forms were developed depending whether the study participants were managed medically or undergo intervention and cardiac surgery.

4.7.5 DEATHS DURING THE STUDY PERIOD:

Due to the advanced age of the study participants, it was expected that some patients might die during the study period. In such a situation the data already gathered was retained in the study. Researchers were advised to check on the Hull and East Yorkshire NHS Trust record systems before sending out any follow up appointments. The participant's family and relatives were not approached after their death.

4.8 VARIABLES RECORDED:

The variables recorded for each participant are outlined in the following table 4-1.

Table 4-1: List of variables recorded for each participant included in the study

Patient demographics	Age, Date of Birth, Gender, Height and Weight, BMI
Source of referral	Outpatients/Inpatients
Clinical Diagnosis	Stable Angina, Unstable Angina, NSTEMI, STEMI
Presenting Symptoms/Signs	CCS angina Class, NYHA Class, Vital Signs- Pulse, Blood pressure, Clinical examination, Previous h/o MI, Previous h/o PCI, Previous h/o CABG bypass surgery, h/o cardiac device implantation
Risk Scores	KILLIP Class (I-IV), GRACE Score mortality risk at 6 month,01 year, EUROSCORE II,
Co-morbid conditions	CHARLSON Comorbidity Index score
Medications	Medication with dosages at each visit
Investigations- ECG	ST elevation, ST depression, AF/Sinus rhythm, Other
Investigations-Bloods	Full Blood Count, Serum Urea and Electrolytes, e-GFR , LFT (Normal/Abnormal), Serum Albumin, High sensitivity CRP, Vitamin D Level, NT-proBNP level
Investigations-Echocardiography	LV function- Normal/Mild/Moderately/Severely impaired, Pulmonary artery systolic pressure/pulmonary hypertension Any valvular abnormality
Investigation-Coronary Angiogram	Site of disease- Left main stem (LMS), Left anterior descending artery (LAD), Left circumflex artery (LCX), Right coronary artery (RCA), Degree of disease- All lesions >50% stenosis, Single/Double/Triple/Left main stem disease
Multi-disciplinary team discussion results	For Percutaneous coronary intervention, For cardiac bypass surgery, For medical therapy
Intervention- PCI	PCI to LMS, PCI to LAD, PCI to LCX, PCI to RCA, Details of stent used- length/bare metal stent/drug eluding stent, Revascularisation- complete/incomplete
Surgery- CABG	LIMA (Left internal mammary artery) to LAD graft, SVG(Saphenous Venous graft) to LCX graft, SVG to RCA, RIMA (Right internal mammary artery graft) to RCA , Other graft details, Revascularisation-complete/incomplete
Outcomes/Complications	Length of hospital stay, Re-hospitalisation, Incidence of death, stroke, transient ischemic attack (TIA), Acute kidney Injury, Major bleeding, Transfusion needed, BARC type, Site of bleeding
Fried phenotype scale	Fried scale at baseline and follow up
Edmonton scale	Edmonton frailty score at baseline and follow up.
Short Form SF-12	SF12 score at baseline and follow up

4.9 DATA ANALYSIS:

The study was reported according to STROBE guidance - http://www.strobe-statement.org/fileadmin/Strobe/uploads/checklists/STROBE_checklist_v4_cohort.pdf. Continuous variables were expressed as mean and standard deviation or median with inter-quartile range and categorical data expressed as numbers/percentages. The relationship of frailty (measured by Fried and Edmonton Frail scale) and pre-specified variables of quality of life (QoL) measured by the SF-12 summary score, as a primary analysis, were evaluated using both simple linear regression and multiple linear regression models. Transformations were not used to meet the model assumptions. Missing values were omitted. Pre-specified variables include: age, sex, body mass index, Fried Frailty index, the Edmonton frail scale, albumin, CRP, vitamin D levels, NT-proBNP and left ventricular function. The study variables were chosen on the basis of previously published work indicating a relationship with change in QoL and which had a plausible biological rationale. Harrell et al(168) suggested 10 subjects per variable for multiple regression analysis. Therefore, based on our sample size of 150 patients a maximum of about 15 variables will be allowed in each analysis. Variables showing a statistically significant relationship in univariate analysis, and those which had previously been shown to have one, even if our data do not confirm this, were entered into the multiple regression model.

In the secondary analysis for categorical outcome variable a logistic regression analysis was used to identify the dependant variables associated with the outcome variable.

The repeated QoL measures were analysed by using repeated measures ANOVA or mixed model and patients were included as random effect. There was no planned subgroup analyses. Missing data were recorded.

The incidence rate of each outcome variable was calculated. Time to outcome was analysed using a Cox-regression model including frailty as an explanatory variable. The association between the pre-specified variables and outcome was investigated using Cox-regression model. The relative risk was expressed as a hazard ratio (HR) with a 95% confidence interval. The Kaplan-Meier analysis and log-rank test were used. An arbitrary level of 5% statistical significance (two-tailed) was used.

4.10 OPERATIONAL DEFINITIONS:

Definitions of some of the important terms used in the study are as follow.

4.10.1 ACUTE MYOCARDIAL INFARCTION (MI)(169)

Acute myocardial infarction was defined as per the universal definition of myocardial infarction. MI required a rise or fall of cardiac troponin with at least one value above the upper reference limit together with at least one of the following:

- Symptoms of ischemia
- ECG changes suggestive of new ischemia
- Development of pathological Q waves on ECG.
- Imaging evidence of new loss of viable myocardium or new regional motion wall abnormality.
- Identification of intracoronary thrombus by angiography.
- Percutaneous coronary intervention (PCI) related MI was defined by elevation of cardiac troponin (cTn) values (>5 × 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cardiac troponin values >20% if the baseline values were elevated and were stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia or (ii) new ischemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality were required.
- Coronary artery bypass grafting (CABG) related MI was defined by elevation of cardiac biomarker values (>10 × 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

4.10.2 ACUTE CEREBROVASCULAR ACCIDENT (CVA)

Acute cerebrovascular accident was defined as brain, spinal cord or retinal cell death attributed to ischemia as evidenced by:

- Imaging like computer tomography (CT) scan or magnetic resonance imaging (MRI) scan showing area of focal ischemic injury or bleeding in a defined vascular distribution territory; or

- Clinical evidence of focal neurological deficit persisting for more than 24 hours or until death(170).

4.10.3 TRANSIENT ISCHEMIC ATTACK

Transient ischemic attack (TIA) was operationally defined(171) as a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than 24 hours, and without evidence of acute stroke.

4.10.4 BLEEDING:

Bleeding was defined as per the Bleeding Academic Research Consortium (BARC)(172):

- **Type 1:** bleeding that was not actionable and did not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; included episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

- **Type 2:** any overt, actionable sign of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that did not fit the criteria for type 3, 4, or 5 but did meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) led to hospitalization or increased level of care, or (3) prompted evaluation.

- **Type 3:**

    - Type 3a:

        - Overt bleeding plus haemoglobin drop of 3 to <5 g/dL (provided haemoglobin drop is related to bleed)

        - Any transfusion with overt bleeding

    - Type 3b:

        - Overt bleeding plus haemoglobin drop ≥5 g/dL (provided haemoglobin drop is related to bleed)
        - Cardiac tamponade
        - Bleeding that required surgical intervention for control (excluding dental/nasal/skin/haemorrhoid)
        - Bleeding that required intravenous vasoactive agents
    - Type 3c:
        - Intracranial haemorrhage (did not include micro bleeds or haemorrhagic transformation, did include intraspinal bleed)
        - Subcategories confirmed by autopsy or imaging or lumbar puncture
        - Intraocular bleed compromising vision
- **Type 4:** CABG-related bleeding
    - Perioperative intracranial bleeding within 48 hr.
    - Reoperation after closure of sternotomy for the purpose of controlling bleeding
    - Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period
    - Chest tube output ≥2L within a 24-h period
- **Type 5:** fatal bleeding
    - Type 5a:
        - Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
    - Type 5b:
        - Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

4.10.5 MAJOR BLEEDING:

Major bleeding was defined as BARC Type 3,4 or 5.

4.10.6 HEART FAILURE:

For purpose of this study, heart failure was defined by presence of left ventricular systolic dysfunction on the echocardiogram.

4.10.7 ACUTE KIDNEY INJURY:

Acute kidney injury was defined as per the KDIGO(173, 174) (Kidney Disease improving Global Outcomes) classification:

- **Stage 1:**
  - Rise of ≥26 μmol/l or 0.3 mg/dl in serum creatinine (Cr) within 48 h.
  - Or 50–99% Cr rise from baseline within 7 days (1.50–1.99 × baseline)
  - <0.5 ml/kg/h urine output for more than 6 hours.
- **Stage 2:**
  - 100–199% Cr rise from baseline within 7 days (2.00–2.99 × baseline)
  - <0.5 ml/kg/h for more than 12 hours.
- **Stage 3:**
  - ≥200% Cr rise from baseline within 7 days (≥3.00 × baseline)
  - Or current Cr ≥354 μmol/l, with either: rise of ≥26 μmol/l or 0.3 mg/dl within 48 h or ≥50% Cr rise from baseline within 7 days
  - Or any new requirement for renal replacement therapy
  - <0.3 ml/kg/h for 24 h or anuria for 12 hours.

4.11 CONCLUSION:

In essence FRAIL-HEART study is an exploratory observational study to determine the association of frailty and QoL in CAD patients above eighty years of age. It is designed as a basis for further large scale cohort studies in future.

5 CHAPTER- ASSOCIATION OF FRAILTY AND QUALITY OF LIFE IN OLDER ADULT PATIENTS WITH CORONARY ARTERY DISEASE- BASELINE CROSS SECTIONAL ANALYSIS

5.1 FRAILTY AND CORONARY ARTERY DISEASE IN OLDER ADULT UK POPULATION:

As previously detailed in Chapters 1 and 2, the older population in the UK is increasing and it is estimated that 1 in 10 people over the age of 65, and 1 in 4 people over 85 are 'frail'. The prevalence of CAD rises with advancing age, being more prevalent in males than females(1, 4) (Fig 5-1). However, there is also an increase in co-morbidities and greater risk from complications arising during/following revascularisation.

'Frailty' amalgamates several key processes happening at this age. It takes into account the loss of functional reserves which makes these individuals vulnerable to poor outcomes in face of any physiological stressor like acute coronary syndromes. Frailty, co-morbidity and quality of life (QoL) assessment tools can help us better understand the prognosis of these older patients and in turn provide a basis for evidence-based decision making(67). Quality of life is perhaps more important than longevity in

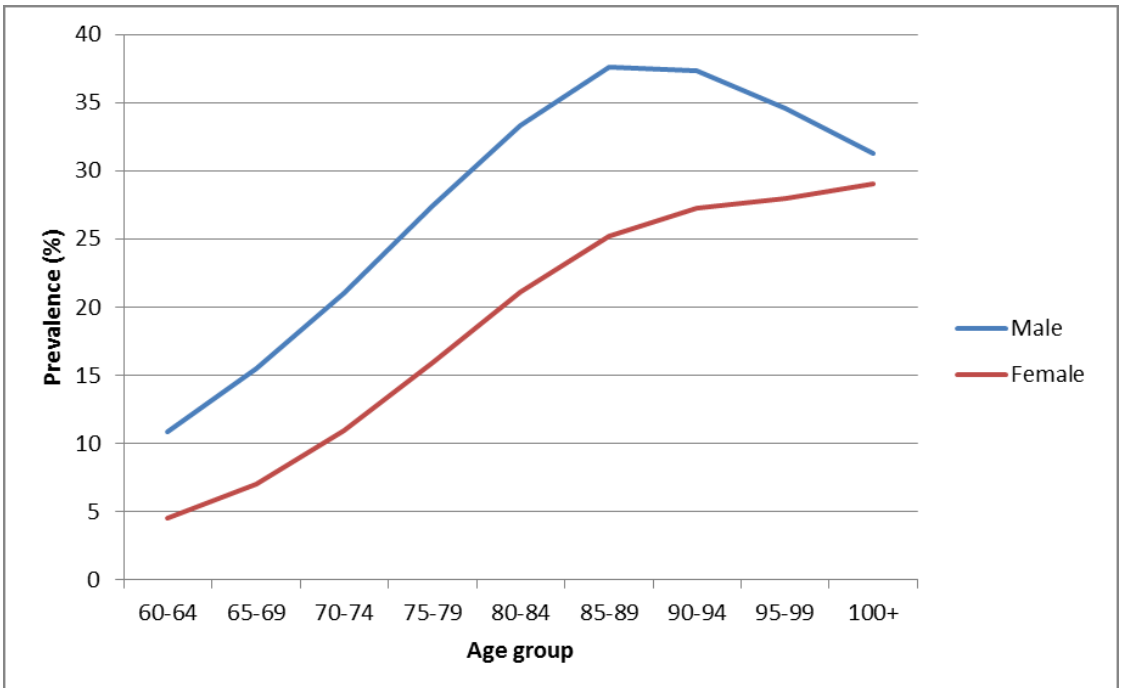


Figure 5-1: Prevalence of coronary artery disease with age and gender. Source: AgeUK and university of Exeter medical school. Melzer et al -The Age UK almanac of disease profile.

individuals of this age. The relationship between QOL and frailty was therefore explored in detail in the FRAIL-HEART study of individuals with CAD aged ≥80years.

5.2 METHODS:

5.2.1 AIMS:

The main aim of this analysis is to determine any association between frailty status of the participant and health related quality of life of patients presenting to their regional cardiac centre (Castlehill Hospital, Hull and East Yorkshire NHS Trust, Cottingham, UK) with acute coronary syndromes as well stable coronary artery disease.

To further understand the impact of frailty on this older population, distribution of frailty across subgroups was studied in detail. Traditionally, co-morbidity has been related with frailty(91). Therefore, we explored the clinical characteristics associated with frailty in this older population with cardiovascular disease.

Fried Frailty Phenotype and Edmonton Frailty scale were used to assess frailty for this analysis. Sensitivity and specificity of these frailty assessment tools was estimated to determine their use as a screening tool in this older population group.

5.2.2 STUDY POPULATION:

The Hull and East Yorkshire Hospitals NHS Trust serve an estimated population of 597,936. This is combined estimated figure for Kingston upon Hull and East Riding of Yorkshire combined for year 2016(2). Around 31,550 were above 80 years of age which

	Total Population (2016)	**Population Over 80 years age (2016)**		
		Total	**Male**	**Female**
East Riding of Yorkshire	337,696	21,440 (6.3%)	8612 (40.2%)	12828 (59.8%)
Kingston Upon Hull	260,240	10,110 (3.9%)	3929 (39.9%)	6181 (61.1%)
Total Catchment population	597,936	31550 (5.3%)	12541 (39.7%)	19009 (60.3%)
Estimated population with coronary artery disease using national prevalence		8860 (1.5%)	4202 (33.5% of 12541) (47.4%)	4658 (24.5% of 19009) (52.6%)

Table 5-1: Estimated population over 80 years of age living in the cohort area. Estimated figures for year 2016.

comprised around 5.3% of the estimated population. The averaged prevalence of coronary artery disease in over eighty years age adults is estimated around 33.5% (range 30-37%) in males and 24.5% (range 20-29%) in females(2). Based on this information, table 5.1 depicts the estimated number of patients living in the cohort area in 2016 as a guided estimate. In addition, the cardiology service provides a tertiary referral service for the surrounding region, including a primary PCI service as well as cardiac surgery. The estimated regional population totals around 1.2 million individuals.

5.2.3 STUDY'S PATIENT FLOW:

This analysis comprised 150 patients enrolled in the FRAIL-HEART study. The study inclusion and exclusion criteria, as well as the methodology have been described in detail in Chapter 4. Figure 5-2 shows the flow of patients through the recruitment process.

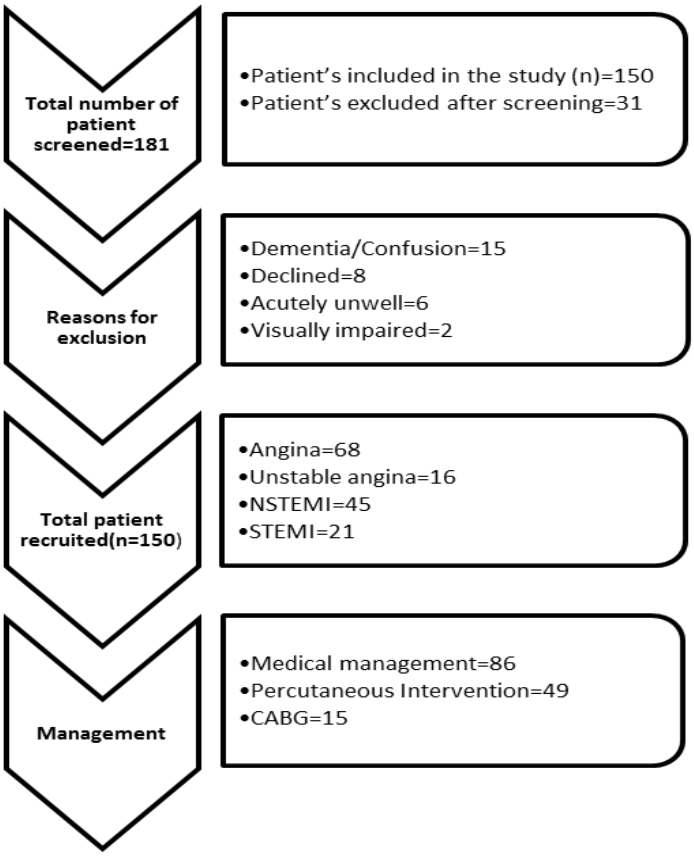


Figure 5-2: Flow diagram showing recruitment process including patients excluded after initial screening process.

5.2.4 STATISTICAL ANALYSIS:

The statistical analysis was done using the IBM SPSS version 24 program (Statistical Package for Social Sciences) and at times STATA 14 program. The data was initially cleaned to remove any inconsistencies. Missing values were identified and excluded

from the analysis. Descriptive statistics of the variables were explored. Normally distributed continuous variables were expressed in terms of means with standard deviation and confidence intervals. Continuous variables that were not normally distributed were expressed as medians with their interquartile ranges. Patient were categorised into non-frail, pre-frail and frail depending upon their Fried frailty phenotype scores. Demographic and clinical variables were used to further define the characteristics of patients in each of these groups. Chi-square test was used to compare the groups where the variable was categorical in nature. ANOVA test was used to compare variables which were of continuous nature. Similar comparison was carried out on the results of Edmonton frailty scores. The frailty scores were used as categorical outcome variable for the analysis. However, aggregate scores of the Fried frailty phenotype and Edmonton frailty score were also generated and used to generate the ROC curves. The physical composite score (PCS) and the mental composite score (MCS) were generated from the SF-12 forms using a dedicated software acquired from the programme software company. The PCS and MCS scores were used as continuous outcome variables. The SF-12 software also generated a categorised outcome grading the PCS and MCS scores as 'at or above average' 'below average and 'far below average'. Initially a simple linear regression model was used to determine the association between frailty and health related quality of life. Then, stepwise linear regression model was used to explore any association of various explanatory variables with the outcome. Assumptions for the regression model were checked using residual normality and variance plots. Receiver operator curve (ROC) curve were generated to explore the sensitivity and specificity of Fried frailty phenotype and Edmonton frailty scale assessment tools in determining health related QoL.

5.3 RESULTS:

5.3.1 STUDY COHORT BASIC CHARACTERISTICS:

The analysis included 150 participants recruited between June 2016 and January 2017. All of the patients were 80 years and above. The mean patient age was 83.7±3.2 (CI 83.1-84.1) years. The maximum age was 97 years. Ninety nine (66%) participants were male and 51 (34%) were females. No study specific reason for this difference in gender uptake was identified. The basic characteristics of the study cohort are listed in Table 5.2 below. Maximum effort was made to approach consecutive patients and their distribution seem to be balanced across inpatients (n=74) and outpatients department (n=76). The average BMI of the cohort was 27.3±4.7. The males had a slightly higher BMI (27.6±4.8) compared to females (26.7±4.4). As expected the average Charlson's

comorbidity index was high at 6.5±2.24. but with no difference with relation to sex (6.7 in males vs 6.1 in females, p=0.12). Sixty eight percent of the participants in the study had treated hypertension while 26.7% had history of diabetes mellitus. This included patients with both insulin and medication treated diabetes but excluded diet controlled diabetics. History of previous myocardial infarction was found in 43.3%; 35.3% gave history of previous coronary stent implantation; and 12% had previous CABG surgery. The rate of previous myocardial infarction was higher in males than females (49.5% vs 31.4%, p=0.03). Patients with significant or decompensated heart failure were excluded from the study as the focus was on patients with CAD. Hence, only 11.3% of the patients included in the study gave history of heart failure. Around 46% of the participants had significant renal disease with creatinine clearance of less than 50.

5.3.2 DISCUSSION ON COHORT BASIC CHARACTERISTICS.

As described in the previous chapter, every effort was made to recruit patient consecutively into the study. In essence the cohort represent a snapshot of the patients presenting to our centre in the north of UK. Generalization of results to the older adult population in general should be with caution. As in other studies of CAD, females comprised a smaller proportion of the study participants than males. No study specific reason for this difference in gender uptake was identified. Recruitment of female patients into clinical studies including cardiovascular trials have traditionally been difficult(175). Different hypothesis have been put forward to explain this sex difference. It may reflect a lower prevalence of symptomatic CAD in females at this age. Outpatients were referred to the hospital by their general practitioner while the hospital has an open-door policy. A referral selection bias cannot be ruled out as it is well known that females can have atypical symptoms of CAD(176).

The prevalence of diabetes has doubled over the last twenty years in UK(177). In the UK PCI registry of all patients treated with PCI, diabetes mellitus has increased from 17.5% in 2007 up to 23.5% in 2017. Our older all-comers patient population had an even higher rate of diabetes (26.7%). Diabetes mellitus is an important risk factor for the development of CAD. Ness et al evaluated a hospital-based practice of diabetic patients with a mean age of 80 years and found that 44% of them were known to have CAD(178).

		Basic characteristics of cohort Total (n=150) Mean±SD (CI)/(%)
Age		83.7±3.2 (83.1-84.1)
Sex	**Male**	99 (66%)
	Female	51 (34%)
BMI		27.3±4.7 (26.5-28.0)
h/o hypertension		102 (68%)
h/o Diabetes mellitus		40 (26.7%)
h/o previous MI		65 (43.3%)
h/o previous PCI		53 (35.3%)
h/o CABG		18 (12%)
h/o Device implantation (PPM/ICD/CRT-D)		13 (8.7%)
h/o Heart Failure		17 (11.3%)
Charlson's Comorbidity score		6.5±2.24 (6.2-6.4)

Table 5-2: Basic Characteristics of the study cohort including demographics.

5.3.3 STUDY COHORT CLINICAL CHARACTERISTICS.

The clinical characteristics of the study participants are detailed in Table 5-3. The study cohort comprised of both inpatients and outpatient participants covering the whole spectrum of acute coronary syndrome. Out of the total cohort of 150 participants, 68 (45.3%) were diagnosed with stable angina, 45(30%) of patients presented with NSTEMI, 21(14%) were diagnosed with STEMI and 16(10.7%) had unstable angina. The incidence of these diagnoses were evenly matched across the two gender groups in the study.

CCS angina classification was used to grade the intensity of angina symptoms of the cohort. Majority of the study participants had mild to moderate restriction (Class II + III, 60.6%) of life style due to angina. Twelve (8.0%) patients did not have any chest pain or presented with atypical symptoms. NYHA classification was used to grade the degree of shortness of breath of the study participants. Again majority (58.0%) had moderate restriction of their lifestyle due to breathlessness. Patients with established heart failure were excluded from the study. However, 31(27.1%) developed moderate to severe left ventricular dysfunction during the course of the study. This figure is likely to be underestimated as only 114 out of the 150 study participants had echocardiogram performed.

When it came to management strategies 56.0% of the patients were treated medically while 34.0% underwent percutaneous revascularisation and 15 patients (10.0%) had CABG surgery performed. The predicted one year mortality by GRACE score was

15.2±14.7% and the average operative mortality risk for the study cohort was 4.96±4.8%, calculated by EUROScore II.

5.3.4 DISCUSSION ON CLINICAL CHARACTERISTICS.

All the established risk assessment models used in the study like Charlson comorbidity, GRACE and Euroscore II suggest the study cohort as a high risk group for poor outcome. The Charlson comorbidity score is used to predict 10 year survival rates in patients with a number of comorbid conditions and has been validated in patients hospitalised with acute coronary syndrome(179). Patients with scores of 5 or more are on the highest tier of risk and their estimated 10 year survival rate is around 21%(180). The average Charlson comorbidity score is our population was therefore high at 6.5±2.5. The GRACE score estimated the cohort's predicted 1 year mortality rate to be 15.2%. Similarly operative mortality risk using Euroscore II estimated a surgical mortality rate of 5.0%. Very high risk patients are commonly "turned down" for CABG surgery and indeed only a relatively small proportion (10%) of the study participants underwent CABG surgery.

		Clinical Characteristics of the cohort Total(n=150) Mean±SD (CI) (%)
Diagnosis	**Stable Angina**	68 (45.3%)
	Unstable Angina	16 (10.7%)
	NSTEMI	45 (30%)
	STEMI	21 (14%)
CCS Angina Class-Baseline	**CCS class I**	19 (12.7%)
	CCS class II	41 (27.3%)
	CCS class III	50 (33.3%)
	CCS class IV	28 (18.7%)
	No chest pain	12 (8%)
NYHA Class-Baseline	**NYHA Class I**	10 (6.7%)
	NYHA Class II	87 (58%)
	NYHA Class III	44 (29.35%)
	NYHA Class IV	9 (6%)
Management	**Medical**	84 (56.0%)
	PCI	51 (34.0%)
	CABG	15 (10%)
GRACE In-hospital mortality		5.2±8.6% (12.8-17.5)
GRACE 1yr mortality		15.2±14.7% (12.8-17.5)
GRACE 3yr mortality		34.5±20.3% (31.2-37.8)
EuroScore II		4.96±4.8% (4.2-5.7%)

Table 5-3: Clinical characteristics of the cohort at baseline including management strategies and risk scores.

The most common patient management approach was conservative (56%), followed by PCI(34%) and CABG(10%). It should be remembered that this study is not

randomised and is not designed to be used to compare the outcomes of different management strategies. The risk profile and disease characteristics of the patients offered different management strategies is highly variable and does not take into account factors such as patients "turned down" for revascularisation due to procedural risk.

5.3.5 BASELINE INVESTIGATIONS OF STUDY COHORT.

The results of the baseline investigation of the study participants are enumerated in Table 5-4. Detailed discussion on the blood investigations and their relationship have been discussed in Chapter 7.

Baseline Investigations of the study cohort		Total(n=150) Mean±SD (CI) (%)
ECG	**Sinus Rhythm**	126 (84%)
	Atrial Fib/Flutter	24 (16%)
	LBBB	13 (8.7%)
	RBBB	11 (7.3%)
	ST depression	13 (8.7%)
	T wave inversion	27 (18%)
	ST elevation	19 (12.7%)
ECHO (n=114)	**Normal LV function**	55 (48.2%)
	Mildly impaired	25 (21.9%)
	Moderately impaired	20 (17.5%)
	Severely impaired	11 (9.6%)
	Normal PASP(<25mmhg)	54 (47.4%)
	Mild elevated PASP(25-40mmhg)	12 (10.5%)
	Mod to severely elevated PASP (>40mmhg)	15 (13.2%)

Table 5-4 : Results of the baseline investigations of the study cohort. Vitamin D and CRP levels were recorded at follow up once acute phase of presentation was over

5.3.6 FAILTY AND QUALITY OF LIFE PROFILE OF STUDY COHORT.

Fried frailty phenotype and Edmonton frailty score were used to assess study participants for frailty. As per Fried Frailty phenotype, 42(28%) of the participants were frail while 89(59.3%) were pre-frail and 19(12.7%) were not frail. Edmonton frailty score further subdivided frail group into mild, moderate and severe frailty. By Edmonton frailty score 39(26.1%) of the participants were frail while 33 (22%) were considered vulnerable and 78(52%) were not frail. Quality of life was measured using SF-12 forms which gave a physical QoL composite score (PCS) and a mental QoL composite score (MCS). The software used to generate these scores also compared them with expected age and sex-matched population scores. The mean physical composite score for the study was 37.1±10.7. 65.3% of the participant's PCS score was far below the expected average. The average mental composite score was 51.7±11.3 and 75.3% of the participant's score was at or above the average. Please refer to Table 5-5.

Female participants as a group were comparable to males in majority of their demographic and clinical characteristics. However they were frailer as a group

		Frailty & QoL Profile of the cohort Total (n=150) Mean±SD (CI) (%)
Fried Score baseline	**Not Frail**	19 (12.7%)
	Pre-Frail	89 (59.3%)
	Frail	42 (28.0%)
Edmonton Score baseline	**Not Frail**	78 (52%)
	Vulnerable	33 (22%)
	Mild Frailty	19 (12.7%)
	Moderate Frailty	13 (8.7%)
	Severe Frailty	7 (4.7%)
SF-12 Physical composite score (PCS) baseline		37.1±10.7 (35.3-38.8)
SF-12 Mental composite score (MCS) baseline		51.7±11.3 (49.9-53.6)
PCS score by category	**At or above**	36 (24%)
	Below	16 (10.7%)
	Far below	98 (65.3%)
MCS score by category	**At or above**	113 (75.3%)
	Below	10 (6.7%)
	Far below	27 (18%)

Table 5-5: Frailty and Quality of life profile of the cohort at baseline.

compared to male participants. This difference was picked up both by Fried frailty phenotype (p= 0.07) and Edmonton frailty score (p= 0.03) and gained significance

with the later. At baseline, the proportion of frail patients calculated using Fried frailty phenotype (n=42, 28%) and Edmonton frailty scale (n=39, 26.1%) were comparable.

5.3.7 OVERLAP BETWEEN FRAILTY, COMORBIDITY AND DISABILITY.

As described in introductory chapters, there is a co-existence between frailty, comorbidity and disability in patients with significant illness. To determine this overlap in our study cohort we defined comorbidity as having at least one major comorbid condition as per Charlson comorbidity score(180). Disability as defined as at least one disability determined by the IADL(181) (Independent activity of daily living) score collected as part of Edmonton frailty scale. Frailty as already stated was determined by Fried frailty score. In our cohort of 150 patients, 28% (n=42 by Fried frailty phenotype) were frail. Out of these 85.7% (n=36) had at least one major comorbidity as per the Charlson comorbidity score. Same proportion of frail patients i.e. 85.7% (n=36) had at least one disability calculated from their IADLs (instrumental activity of daily living score). In 71.4% (n=30) of the frail patients there was an overlap of all the three factors which formed 20% of whole cohort. This has been demonstrated in the Venn diagram (figure 5-3) constructed on lines similar to the one used by Fried et al in their original article(46).

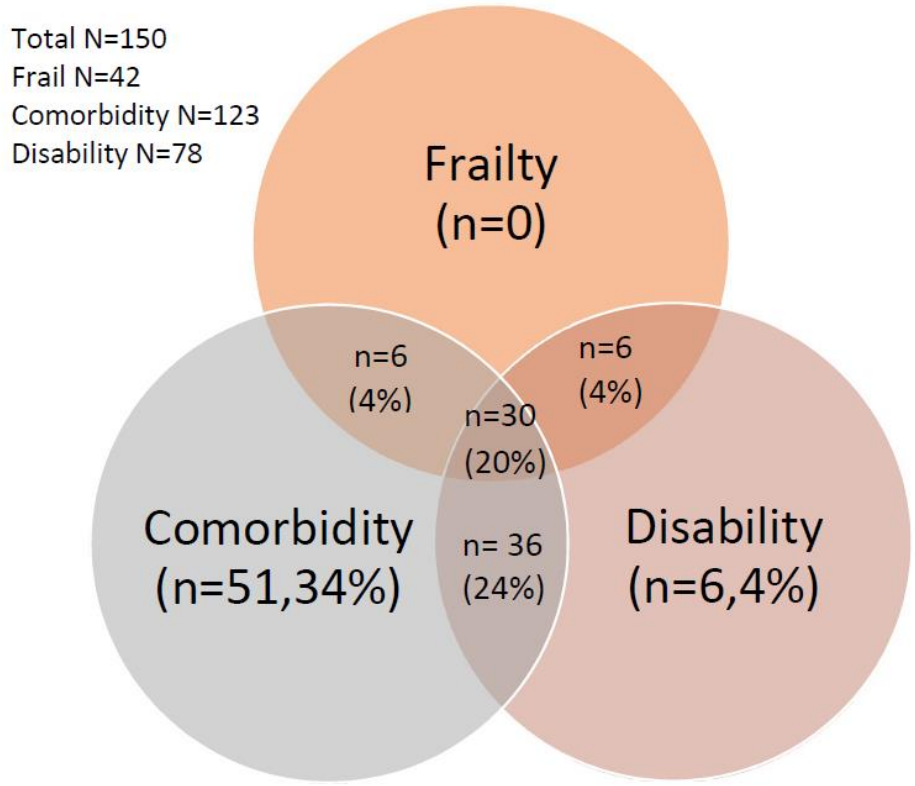


Figure 5-3: Venn diagram showing overlap of frailty, disability and comorbidity. Frailty was derived from Fried frailty phenotype. Disability was derived from IADLs scores and Comorbidity was calculated from Charlson comorbidity scores.

5.3.8 DISCUSSION ON FRAILTY COMORBIDITY OVERLAP.

Fried et al reported an overlap of 46.2% in their landmark article in 2001(46), more recently Wong et al reported an overlap of 82% in older community dwelling cohort(182). As the burden of comorbidity and disability increases with age it is expected that the overlap will be significant. In our study there were no frail participant who didn't have with a comorbidity or a disability. The study was conducted on cohort presenting with symptomatic coronary artery disease and 44% presented with myocardial infarction which would add to the overlap. For this reason for this analysis present admission with MI was not counted in comorbidity. It also indicates that any benefit expected from frailty intervention in this age group will be limited to some extent by the comorbidities and disabilities which will also need to be addressed.

5.3.9 ANALYSIS OF FRAILTY SCORES AND THEIR RELATIONSHIP TO CLINICAL ATTRIBUTES.

Two frailty scores were used to assess the study population namely Fried frailty phenotype and Edmonton scale. To get better understanding of the clinical characteristics of frail population in our study, we further explored the data of the frailty sub groups. The analyses are detailed in Table 5.5 and 5.6 below at end of the description.

Fried frailty phenotype score results categorised the cohort into frail, pre-frail and non-frail subgroups. We explored the attributes of these subgroups and compared them. The frail group was generally older. The mean age of the frail group was 84.4±3.4 years compared to non-frail group whose average age was 82.2±1.8 years. The BMI score was similar in frail and non-frail group in our cohort (26.2±2.8 vs 27.9±5.5, p=0.41). Charlson comorbidity score suggested a higher comorbidity burden in the frail group compared to non-frail (5.9±1.6 vs 7.5±2.4, p=0.005).

There was no suggestion that frail participants were presenting more with ACS and various diagnoses of coronary artery disease were evenly spread across the frailty subgroups. 16.7% of the frail patients presented with STEMI compared to 10.5% in non-frail group. Similarly, 38.1% of the frail group presented with NSTEMI and 26.3% of the non-frail sub-group presented with same condition.

There was a higher symptom load noted in frail subgroup. 66.7% of the frail patients had angina CCS class III and IV symptoms compared to 21% of patients in non-frail

group (p=0.03). Similar was the case with breathlessness, only 15.8% of the non-frail group patients complained of NYHA Class III and IV symptoms while 54.8% of the frail patients had Class III and IV symptoms (p=0.000).

Majority of the study participants were in sinus rhythm (84%) despite higher prevalence of atrial fibrillation in older adult population in general. Around 16% of the study participants had atrial fibrillation/flutter on their ECGs. Of these, 11 (26.2%) of the frail patients had atrial fibrillation or flutter compared to only 2 (10.5%) of non-frail patient group. There was no significant difference in management strategies across the three frailty subgroups. Twenty three (54.8%) of the frail patients were treated medically and 18(42.9%) had PCI compared to 10(52.6%) and 8(42.1%) of non-frail patients who had medical therapy and PCI respectively.

The frail subgroup of patient had the highest risk profile compared to pre-frail and non-frail groups. The predicted one year mortality rate by GRACE score for the frail group was 20 %(14-27%) compared to non-frail which had 11 %(7-14%) and pre-frail which had 14 %(11-16%) one year predicted mortality rate. Similarly Charlson's comorbidity score was higher for the frail group (see table 5-6).

The frail group also had lower physical and mental composite score for quality of life compared to pre-frail and non-frail group. The mean SF-12 PCS score for frail group was 30.5±7.1 compared to 38.8±11.3 and 43.5±10.7 for pre-frail and non-frail group respectively (p=0.005). The mental composite score for quality of life was also lowest for the frail subgroup. The SF-12 MCS score for frail patients was 47.4±12.8 compared to pre-frail which had score of 52.7±10.7 and non-frail group who's score was 57.1±6.4 (p=0.003).

		Fried Frailty Phenotype			
		Non-frail (n=19)	Prefrail (n=89)	Frail (n=42)	p Value
		Mean±SD/(%)	Mean±SD/(%)	Mean±SD/(%)	
Age		82.2±1.8 (81.3-83.0)	83.6±3.3 (82.9-84.3)	84.4±3.4 (83.3-85.4)	.043
Gender	**Female**	3 (15.8%)	29 (32.6%)	19 (45.2%)	.072
	Male	16 (84.2%)	60 (67.4%)	23 (54.8%)	
BMI		26.2±2.8 (24.9-27.6)	27.2±4.6 (26.2-28.1)	27.9±5.5 (26.2-29.6)	.411
h/o hypertension		13 (68.4%)	61 (68.5%)	28 (66.7%)	.976
h/o Diabetes mellitus		4 (21.1%)	25 (28.1%)	11 (26.2%)	.265
GRACE 1yr mortality		11±7% (7-14%)	14±12% (11-16%)	20±20 (14-27%)	.014
Charlson's Comorbidity score		5.9±1.6 (5.2-6.7)	6.2±2.2 (5.8-6.7)	7.5±2.4 (6.7-8.2)	.005
SF-12 PCS score baseline		43.5±7.6 (39.8-47.1)	38.8±11.3 (36.4-41.2)	30.5±7.1 (28.3-32.7)	.005
SF-12 MCS score baseline		57.1±6.4 (54.0-60.2)	52.7±10.7 (50.4-54.9)	47.4±12.8 (43.4-51.4)	.003

Table 5-6 : Demographic and quality of life characteristics of the frailty subgroups according to Fried Frailty Phenotype

		Fried Frailty Phenotype			
		Non-frail (n=19) n/(%)	Prefrail (n=89) n/(%)	Frail (n=42) n/(%)	p Value
Diagnosis	**Angina**	10 (52.6%)	44 (49.4%)	14 (33.3%)	0.73
	Unstable Angina	2(10.5%)	9 (10.1%)	5 (11.9%)	
	NSTEMI	5 (26.3%)	24 (26.9%)	16 (38.1%)	
	STEMI	2 (10.52%)	12 (13.5%)	7 (16.7%)	
CCS Angina Class-Baseline	**No chest pain**	2(10.5%)	6(6.7%)	4 (9.5%)	.030
	CCS class I	4 (21.1%)	9 (10.1%)	6 (14.3%)	
	CCS class II	9 (47.4%)	28 (31.5%)	4 (9.5%)	
	CCS class III	2 (10.5%)	32 (36.0%)	16 (38.1%)	
	CCS class IV	2 (10.5%)	14 (15.7%)	12(28.6%)	
NYHA Class-Baseline	**NYHA Class I**	4 (21.1%)	6 (6.7%)	0 (0%)	<.001
	NYHA Class II	12 (63.2%)	58 (65.2%)	17 (40.5%)	
	NYHA Class III	3 (15.8%)	24 (27.0%)	17 (40.5%)	
	NYHA Class IV	0 (0%)	1 (1.1%)	8 (19.0%)	
ECG	**Sinus Rhythm**	17 (89.5%)	78 (87.6%)	31 (73.8%)	.103
	Atrial Fib/Flut	2 (10.5%)	11 (12.4%)	11 (26.2%)	
LV function (n=114)	**Normal**	7 (46.7%)	29 (45.3%)	20 (57.1%)	.520
	Mildly impaired	2 (13.3%)	15 (23.4%)	9 (25.7%)	
	Moderately impaired	3 (20%)	12 (18.8%)	5 (14.3%)	
	Severely impaired	3 (20.0%)	8 (12.5%)	1 (2.9%)	
Management	**Medical**	10 (52.6%)	51 (57.3%)	23 (54.8%)	.132
	PCI	8 (42.1%)	25 (28.1%)	18 (42.9%)	
	CABG	1 (5.3%)	13 (14.6%)	1 (2.4%)	

Table 5-7: Clinical characteristics of the frailty subgroups according to Fried Frailty Phenotype

Similar analysis was carried out using the Edmonton frailty score. The Edmonton frailty score sub-graded frail participants further into mild, moderate and severe frailty. The attributes of the sub group were analysed in the similar manner as fried frailty phenotype. Sub-dividing frail group into further subgroups meant that there were less participants in each subgroups which at times made interpretation of the results difficult. We decided against grouping the subgroups together as this study is a template for a larger cohort study. Furthermore, pre-frail or vulnerable group is the largest group in the study and grouping it to any side will bias the result towards that group. However, the results obtained were comparable to those of fried frailty phenotype described above. For detailed breakdown refer to table 5-7 and 5-8 below.

	Edmonton Frailty Score- baseline					
	Not Frail (n=78)	**Vulnerable (n=33)**	**Mild Frailty (n=19)**	**Moderate Frailty (n=13)**	**Severe Frailty (n=7)**	
	Mean/%	**Mean/%**	**Mean/%**	**Mean/%**	**Mean/%**	**p value**
Age	83.0±2.8 (82.4-83.7)	84.3±3.7 (83.0-85.7)	84.5±3.1 (83.0-86.0)	84.5±4.1 (82.0-86.9)	83.9±2.6 (81.4-86.3)	0.16
Female	19 (24.4%)	11 (33.3%)	11 (57.9%)	6 (46.2%)	4 (57.1%)	0.03
Male	59 (75.6%)	22 (66.7%)	8 (42.1%)	7 (53.8%)	3 (42.9%)	
BMI	27.2±4.0 (26.3-28.1)	27.2±5.2 (25.3-29.0)	27.6±6.4 (24.5-30.7)	27.9±5.3 (24.6-31.1)	26.2±3.0 (23.4-29.0)	0.96
h/o hypertension	54 (69.2%)	23 (69.7%)	11 (57.9%)	8 (61.5%)	6 (85.7%)	0.69
h/o Diabetes mellitus	19 (24.4%)	8 (24.2%)	7 (36.8%)	5 (38.5%)	1 (14.3%)	0.16
GRACE 1yr mortality	12.3±11.5% (9.7-14.9)	16.2±12.4% (11.8-20.6)	21.6±18.3% (12.7-30.4)	16.1±16.6% (6.0-26.1)	23.3±30.7% (-0.5-51.7)	0.06
Charlson comorbidity score	5.9±1.9 (5.5-6.4)	6.9±2.5 (6.0-7.8)	6.6±2.0 (5.6-7.5)	8.5±2.7 (6.9-10.1)	7.9±2.5 (5.6-10.1)	<0.001
SF-12 PCS score baseline	40.6±10.7 (38.2-43.0)	35.9±9.8 (32.5-39.4)	31.4±9.5 (26.8-36.0)	31.4±9.9 (25.4-37.4)	29.5±5.1 (24.7-34.2)	<0.001
SF-12 MCS score baseline	56.5±8.3 (54.7-58.4)	46.5±12.5 (42.1-51.0)	52.8±9.5 (48.2-57.3)	43.2±9.7 (37.3-49.1)	36.0±8.2 (28.4-43.6)	<0.001

Table 5-8: Demographic characteristics and quality of life parameters of study cohort according to Edmonton Frailty score

		Edmonton Frailty Score- baseline					
		Not Frail (n=78)	**Vulnerable (n=33)**	**Mild Frailty (n=19)**	**Moderate Frailty (n=13)**	**Severe Frailty (n=7)**	**p value**
Diagnosis	**Angina**	40 (51.3%)	12 (36.4%)	7 (36.8%)	6 (46.2%)	3 (42.9%)	0.55
	Unstable Angina	8 (10.3%)	6 (18.2%)	1 (5.3%)	1 (7.7%)	0 (0%)	
	NSTEMI	21 (26.9%)	9 (27.3%)	7 (36.8%)	6 (46.2%)	2 (28.6%)	
	STEMI	9 (11.5%)	6 (18.2%)	4 (21.1%)	0 (0%)	2 (28.6%)	
CCS Angina Class-Baseline	**Class I**	14 (17.9%)	2 (6.1%)	2 (10.5%)	0 (0%)	1 (14.3%)	0.36
	Class II	23 (29.5%)	8 (24.2%)	6(31.6%)	4 (30.8%)	0 (0%)	
	Class III	25 (32.1%)	10 (30.3%)	7 (36.8%)	5 (38.5%)	3 (42.9%)	
	Class IV	9 (11.5%)	10 (30.3%)	4 (21.1%)	2 (15.4%)	3 (42.9%)	
	No Chest pain	7 (9.0%)	3(9.1%)	0 (0%)	2 (15.4%)	0 (0%)	
NYHA Class-Baseline	**Class I**	8 (10.3%)	2 (6.1%)	0 (0%)	0 (0%)	0 (0%)	<0.001
	Class II	57 (73.1%)	20 (60.6%)	6 (31.6%)	2 (15.4%)	2 (28.6%)	
	Class III	12 (15.4%)	10 (30.3%)	11 (57.9%)	7 (57.9%)	4 (57.1%)	
	Class IV	1 (1.3%)	1 (3.0%)	2 (10.5%)	4 (30.8%)	1 (30.8%)	
ECG	**Sinus Rhythm**	66 (84.6%)	29 (87.9%)	14 (73.7%)	11 (84.6%)	6 (85.7%)	0.75
	AF	12 (15.4%)	4 (12.1%)	5 (26.3%)	2 (15.4%)	1 (14.3%)	
ECHO-LV dysfunction	**Normal**	29 (48.3%)	12 (46.2%)	8 (57.1%)	4 (40.0%)	3 (75.0%)	0.52
	Mild	11 (18.3%)	9 (34.6%)	3 (21.4%)	3 (30.0%)	0 (0%)	
	Moderate	11 (18.3%)	3 (11.5%)	3 (21.4%)	3 (30.0%)	0 (0%)	
	Severe	9 (15.0%)	2 (7.7%)	0 (0%)	0 (0%)	1 (25.0%)	
Management	**Medical**	44 (56.4%)	15 (45.5%)	12 (63.2%)	9 (69.2%)	4 (57.1%)	0.55
	PCI	25 (32.1%)	13 (39.4%)	7 (36.8%)	3 (23.1%)	3 (42.9%)	
	CABG	9 (11.5%)	5 (15.2%)	0 (0%)	1 (7.7%)	0 (0%)	

Table 5-9: Clinical characteristics of the study cohort according to Edmonton frailty scale.

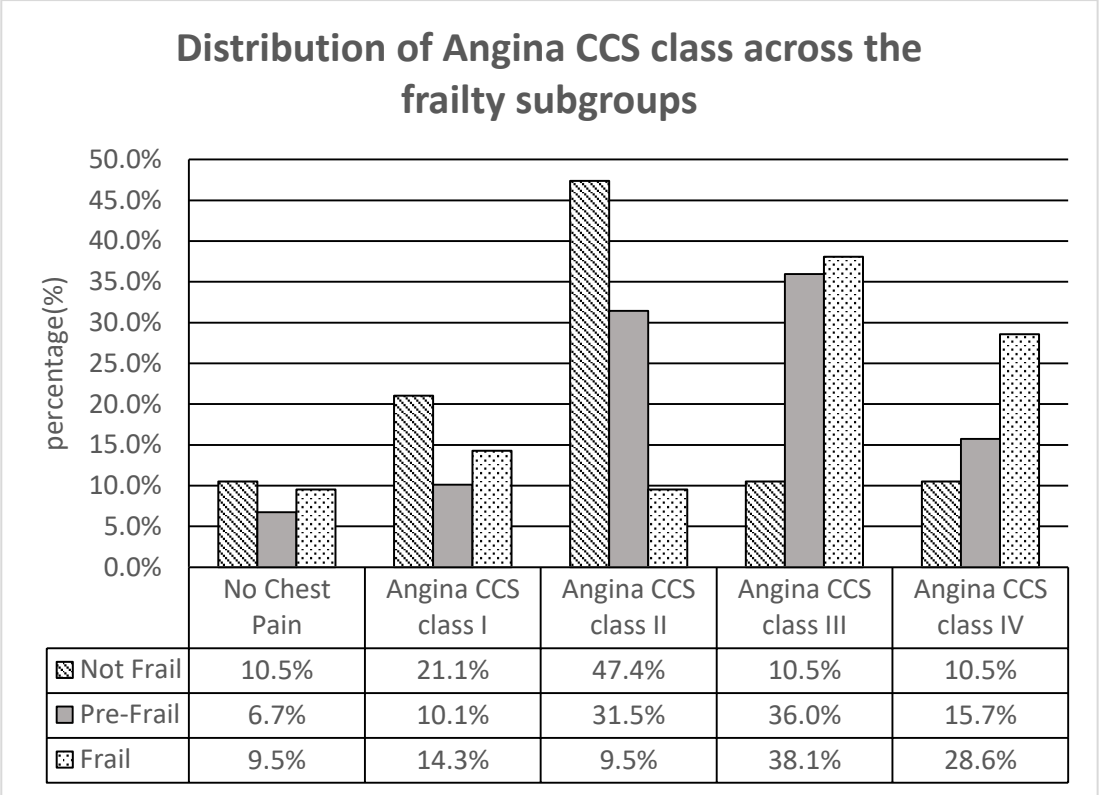


Figure 5-4: Graph showing the distribution of Angina CCS class across the frailty subgroups as per Fried frailty phenotype

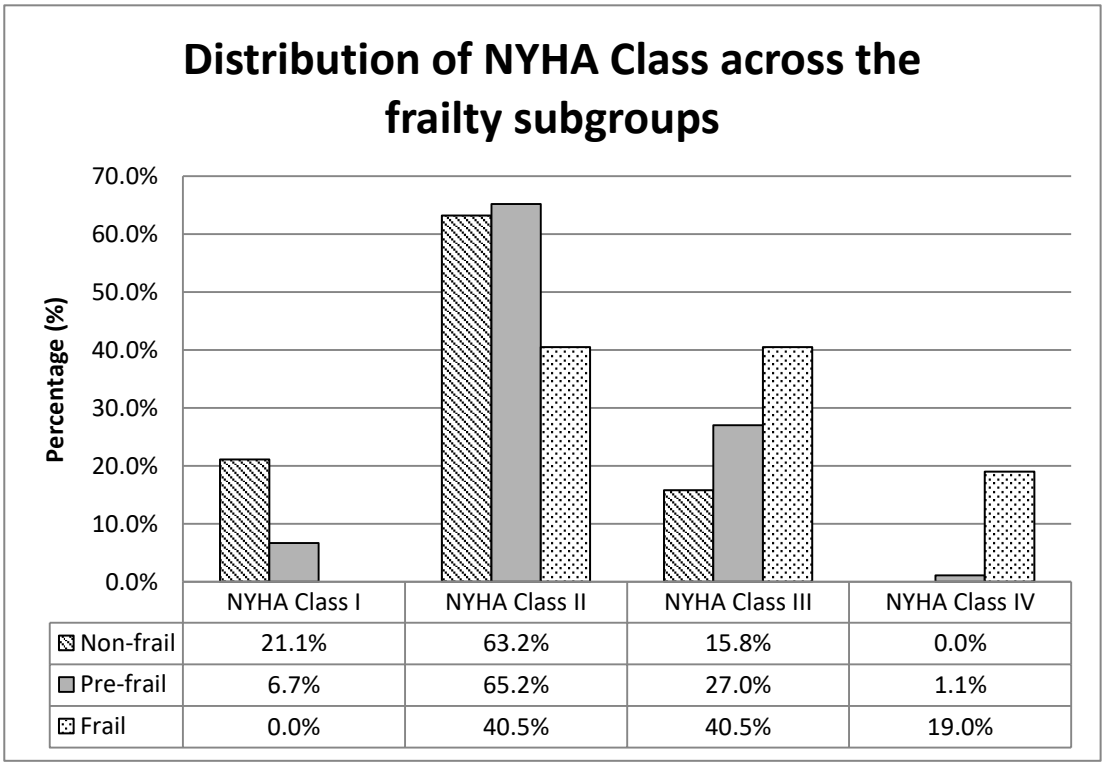


Figure 5-5: Graph showing distribution of NYHA Class across the frailty groups as per Fried frailty phenotype

5.3.10 DISCUSSION ON FRAILTY SCORES ANALYSIS AND FRAILTY ATTRIBUTES.

This analysis helped characterise the demographic and clinical attributes of the frail participants in the study in comparison to participants that were not frail. The findings were consistent both for Fried Frailty phenotype and Edmonton frailty score which adds validity to the analyses. Considerable overlap was found in their findings. As the analysis was done as an exploration and not powered for any significance, these findings have been reported as trends and associations. Both the frailty scores suggested that majority of the participants lay in the pre-frail (59.3%) or the vulnerable/ mild frailty (34.7%) category. These were the people who had some characteristics of frailty but scored below the cut-off point. This group is likely to benefit the most from frailty intervention as they have some frail characteristics but not fully frail.

The mean age of the patients across the frailty subgroups was significantly different as the frail group are the oldest amongst the subgroups. Prevalence of frailty was higher among the female compared to male participants (FFP 37.3% vs 23.2% p=0.07, EFS 41.2% vs 18.2% p=0.03). Unintentional weight loss is assessed as a component in majority of the frailty assessment tools as a marker for poor nutritional status. However the measured BMI across the frailty subgroups in our study, were not significantly different. This emphasises the fact that frail patients may not necessarily look frail and may have normal weight and BMI. Sarcopenia which is described as an underlying process in frailty may not reflect in their body weight or BMI. The caveat with weight assessment in cardiac patients is that with advance cardiac condition patient may have variable degree to heart failure leading to fluid accumulation. Hence the measured body weight may not reflect the actual dry body weight. Overt heart failure patients were excluded from this analysis but patient who developed heart failure during the study duration were included.

The Charlson comorbidity score for frail participants was significantly higher compared to those who were not frail (FFP 5.9±1.6 vs 7.5±2.4 p=0.005, EFS 5.9±1.9 vs 7.9±2.5 p=0.00). This is in keeping with the fact that there is an overlap between frailty and comorbidity which is even more pronounced in older population. The high Charlson comorbidity score would characterize frail as the most high risk group amongst the cohort.

The baseline frailty assessments captured the participants' status before they underwent their respective treatments. STEMI patients were the only subgroup that were included after they had undergone their treatment. Although statistic difference was detected in the angina CCS class and NYHA class across the frailty subgroups but some of the subgroups had too few patients to reliably interpret this difference. Review of their proportion values suggests that frail participants tend to have higher CCS angina and NYHA class symptoms (Figure 5-4 and 5-5). However, it should be bear in mind that we gave patients admitted with STEMI CCS class 4 which may add bias to this result.

By the Fried criteria, there was a trend towards higher proportion of atrial fibrillation or flutter (AF) in frail participants compared to non-frail participants (FFP 26.2% vs 10.5% p=0.103, EFS 20.5% vs 15.4% p=0.75). No attempt was made to interpret the results of LV function due to the fact that patients with heart failure were excluded from the study.

The Charlson comorbidity score is a predictor of the long term (10years) survival rate(180). The Charlson score was first proposed in 1984 and since has been cited over 5500 times and validated in several large scale epidemiological studies(183). It is a weighted index which takes into account the number and seriousness of comorbid disease. GRACE score was used to estimate the short term mortality risk of the study cohort. GRACE score is a well validated risk score to predict mortality in patients presenting with ACS. It was developed on base of a registry of 100,000 patients presenting with ACS across 30 countries(184) .In our study, it was noted that the predicted 1 year mortality rate of the frail participant were significantly higher as compared to non-frail participants (FFP 11%(7-14%) vs 20%(14-27%) p=0.014, EFS 12.3%(9.7-14.9%) vs 16.1%(6.0-25%) p=0.06). This suggested that frailty assessment is able to offer extra risk stratification in addition to conventional risk scores in an already high risk population group of older adult patients with coronary artery disease.

Similarly the prevalence of frailty was twice as much in patients presenting with ACS compared to patient presenting with stable angina (66.7% vs 33.3%) (Figure 5-6). This again may represent the high symptom or disease burden presenting acutely unwell to hospital. The baseline frailty assessment captured patient state 4-6 weeks prior to their presentation.

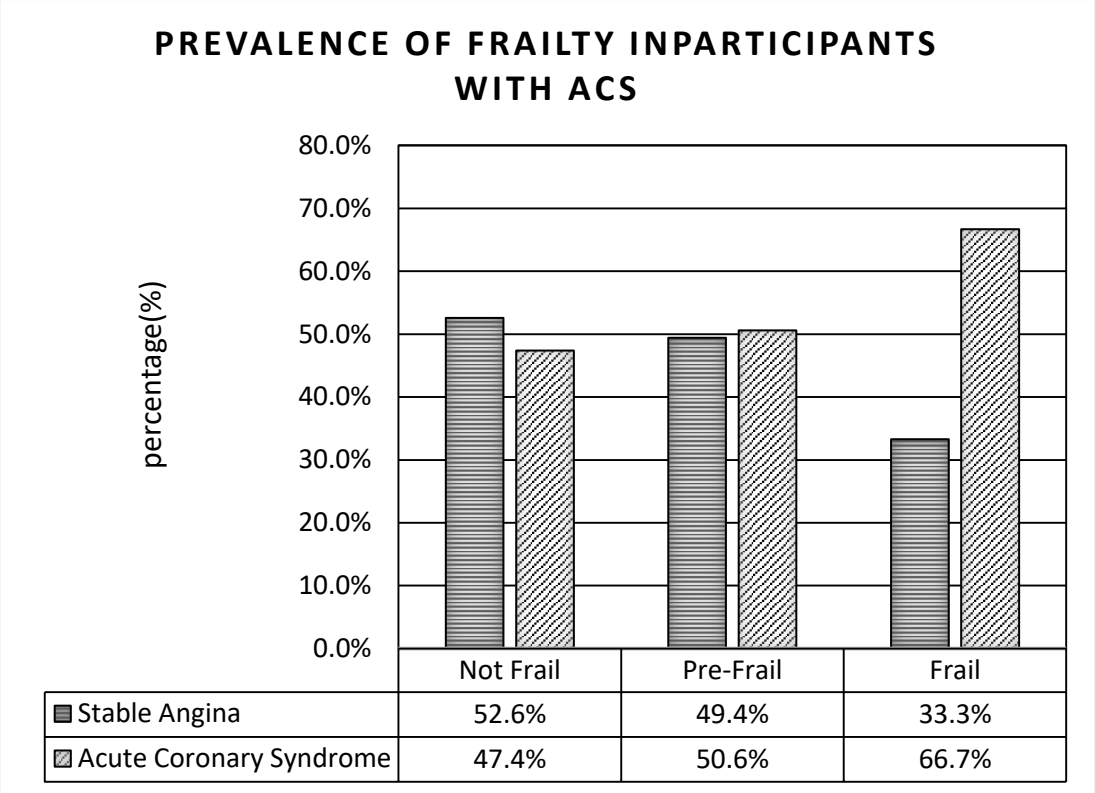


Figure 5-6: Prevalence of frailty in patients presenting with acute coronary syndrome

5.3.11 RELATIONSHIP BETWEEN FRAILTY MEASURES AND QUALITY OF LIFE

Initial tabulated analysis of the variables suggested a significant relationship between frailty status and measures of quality of life measures. This relationship was further explored through linear regression analysis to quantify the strength of this association. Initially multiple linear regression was carried out on baseline variables to determine which variable held a significant association with the outcome variable i.e. the QoL Then a 'Backward stepwise' regression was carried out to narrow down the model. Assumptions for the regression model were also checked to validate the statistical analysis applied.

Multiple Linear regression analysis using the baseline SF-12 physical composite score as the outcome variable showed that the SF-12 PCS score at baseline was significantly or closely associated with female sex, baseline CCS angina class, baseline NYHA class, diagnosis of unstable angina and Fried frailty phenotype baseline score. All of these variables were inversely related with the outcome variable of SF-12 PCS baseline. These variables were further analysed using backward stepwise regression model. This

further improved the strength of their association with the outcome variable and also improved the adjusted R square value of the model to 0.33 (Table 5-10).

Similar analysis was carried out using SF-12 mental composite score at baseline as the outcome variable. Multiple variable regression analysis showed a significant relation between age, Edmonton frailty score and SF-12 mental composite score. Interestingly Fried frailty phenotype failed to detect any significant relationship between frailty and SF-12 mental composite score. The 'Backward stepwise regression' improved the adjusted R square value of the model to 0.369 (Table5-11).

SF-12 PCS baseline	Multiple variable regression (Adj R^2=0.32)		Backwards stepwise regression (Adj R^2=0.33)	
	β (95% CI)	p value	β (95% CI)	p value
Age	-0.12 (-0.66, 0.42)	0.64		
Female	-3.58 (-7.24, 0.59)	**0.05**	-2.90 (-6.11, -0.32)	**0.07**
BMI	-0.14 (-0.51, 0.23)	0.45		
h/o hypertension	-1.15 (-4.66, 2.36)	0.52		
h/o Diabetes Mellitus	-0.90 (-4.79, 2.99)	0.65		
h/o previous MI	0.49 (-4.15, 5.13)	0.84		
h/o previous PCI	-3.82 (-8.22, 0.57)	0.09	-3.15 (-6.34, 0.03)	**0.05**
CCS Angina Class-Baseline				
No angina	0.00	**0.06**	0.00	**0.06**
Class I	-0.68 (-7.34, 7.48)		-0.81 (-7.50, 5.87)	
Class II	-2.31 (-8.78, 4.17)		-3.76 (-9.69, 2.18)	
Class III	-6.14 (-12.34, 0.06)		-6.41 (-16.44, -0.64)	
Class IV	-8.06 (-17.42, 1.31)		-2.67 (-8.76, 3.40)	
NYHA Class- Baseline				
Class I	0.00	**0.04**	0.00	**0.004**
Class II	-4.68 (-11.07, 1.70)		-4.76 (-10.83, 1.32)	
Class III	-8.73 (-15.93, -1.53)		-9.77 (-16.44, -3.12)	
Class IV	-2.27 (-12.53, 7.99)		-2.92 (-12.19, 6.35)	
Charlson's Comorbidity score	-0.74 (-1.47, 0.14)	**0.14**	-0.96 (-1.72, -0.21)	**0.01**
GRACE 1yr mortality	-0.05 (-0.21, 0.11)	0.54		
EUROscore2	0.84 (-0.39, 0.56)	0.73		
Diagnosis				
Stable angina	0.00	0.13		
Unstable Angina	-4.61 (-10.03, 0.81)			
NSTEMI	0.52 (-3.96, 5.00)			
STEMI	6.54 (-3.05, 16.13)			
Fried Score baseline				
Not Frail	0.00	**0.05**	0.00	**0.005**
Pre-Frail	-0.05 (-5.04, 4.94)		-1.44 (-6.05, 3.17)	
Frail	-5.42 (-11.89, 1.04)		-7.29(-12.83,1.75)	
Edmonton frailty score baseline				
Not Frail	0.00	0.82		
Vulnerable	-0.36 (-4.48, 3.76)			
Mild Frailty	-3.01 (-8.36, 2.33)			
Moderate Frailty	0.37 (-6.34, 7.07)			
Severe Frailty	-0.77 (-9.84, 8.29)			

Table 5-10: Multiple variable regression and Backwards stepwise regression showing relation between frailty and SF-12 physical composite score

SF-12 MCS score baseline	Multiple Linear regression (Adj R^2=0.33)		Stepwise Regression (Adj R^2=0.35)	
	β(95%CI)	p value	β (95%CI)	p value
Age	1.01(0.45,1.57)	**0.00**	0.83(0.35,1.32)	**0.00**
Female	-2.09(-5.86,1.69)	0.28		
BMI	-0.05(-0.43,0.33)	0.79		
h/o hypertension	1.85(-1.78,5.49)	0.31		
h/o Diabetes Mellitus	-4.03(-8.07,-0.01)	0.05	-2.74(-6.34,0.89)	**0.03**
h/o previous MI	2.90(-1.90,7.71)	0.23		
h/o previous PCI	-1.87(-6.42,2.68)	0.42		
CCS Angina Class-Baseline				
No angina	0.00	0.52		
Class I	3.14(-4.53,10.81)			
Class II	3.07(-3.64,9.77)			
Class III	0.03(-6.39,6.45)			
Class IV	4.76(-4.93,14.46)			
NYHA Class- Baseline				
Class I	0.00	0.07	0.00	0.20
Class II	0.93(-5.68,7.54)		1.23(-4.85,7.30)	
Class III	6.29(-1.16,13.74)		4.78(-2.05,11.62)	
Class IV	2.73(-7.90,13.35)		0.15(-9.41,9.71)	
Charlson's Comorbidity score	-0.69(-1.72,0.34)	0.19	-0.47(-1.26,0.31)	0.24
GRACE 1yr mortality	-0.08(-0.25,0.92)	0.37		
EUROscore2	-0.10(-0.59,0.40)	0.70		
Diagnosis				
Stable Angina	0.00	0.60		
Unstable Angina	0.70(-4.91,6.31)			
NSTEMI	0.27(-4.37,4.91)			
STEMI	-5.86(-15.8,4.07)			
Fried Score baseline				
Non-Frail	0.00	0.77		
Pre-Frail	-1.70(-6.87,3.47)			
Frail	-0.94(-7.63,5.75)			
Edmonton frailty score baseline				
Non-Frail	0.00	**0.00**	0.00	**0.00**
Vulnerable	-11.45(-15.7,-7.1)		-11.23(-15.11,-7.35)	
Mild Frailty	-4.85(-10.38,0.69)		--5.88(-10.91,-0.85)	
Moderate Frailty	-14.25(-21.19,-7.31)		-14.13(-20.29,-7.96)	
Severe Frailty	-21.63(-31.0,-12.24)		-22.05(-29.52,-14.5)	

Table 5-11: Multiple variable regression and backward stepwise regression showing relationship between frailty and SF-12 Mental composite score

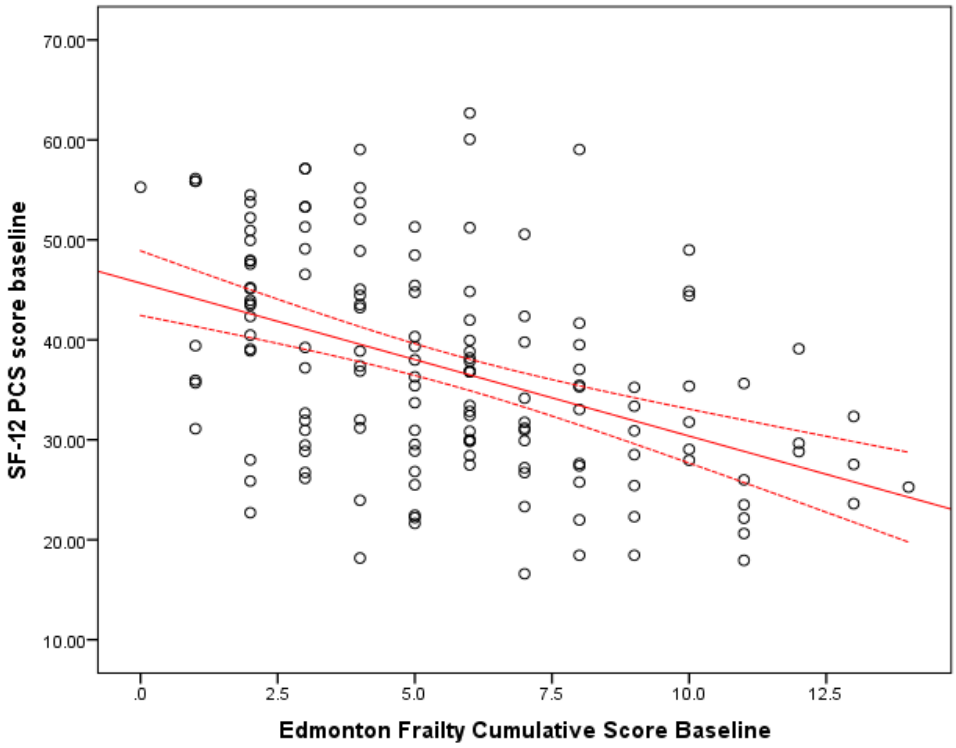
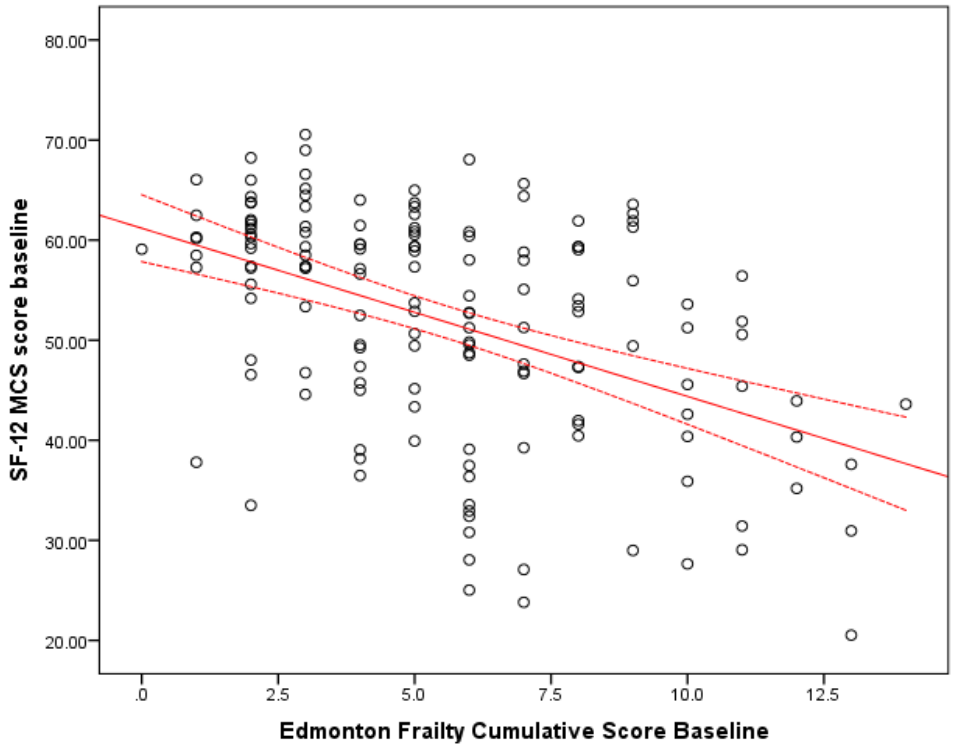


Figure 5-4: Graphs showing inverse relationship between Edmonton frailty score and Quality of Life parameters.



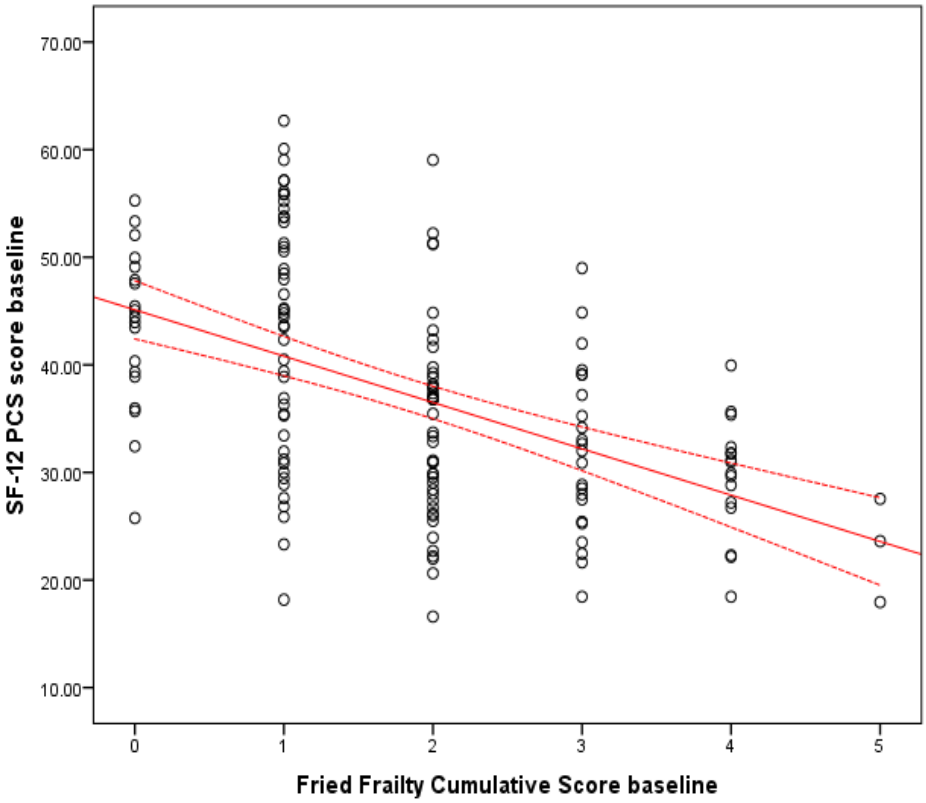
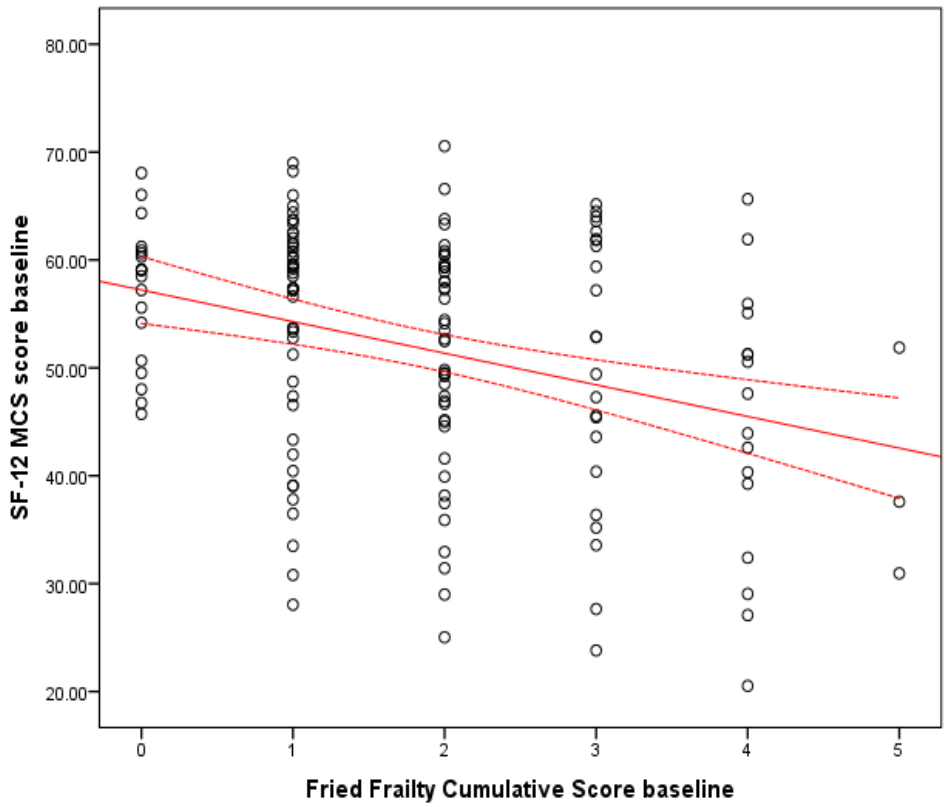


Figure 5-5: Graphs showing inverse relationship between Fried Frailty Phenotype and Quality of Life parameters.



5.3.12 DISCUSSION ON THE PREDICTORS OF QUALITY OF LIFE PARAMETERS.

The main aim of the regression analysis was to determine significant predictors of QoL in this older cohort with coronary artery disease and its relation to frailty. Significant predictors of QoL for both the physical composite score as well as the mental composite score were CCS angina class, NYHA Class, Charlson's comorbidity score and frailty. Both of the regression analysis had good adjusted R values (0.359, 0.369) which means that it can reliably explain the variations in analysed data. These predictors of QoL in this analysis paint a very interesting picture. CCS angina class and NYHA Class were inversely related to both physical and mental parameters of QoL. This indicates that higher symptom burden is related to poor QoL. Hence good symptom control should be an important consideration for management strategy of their coronary artery disease as it will translate into a better QoL. As expected comorbidity effects the quality of life of these patients. However addressing comorbidities may not always be effectively possible at this advance age. Frailty was another consistent predictor variable of QoL. It can be postulated that detailed frailty assessment in these patient may be able to identify domains of deficiency and tailored strategies can be devised to treat them and improve outcomes. This is a topic of present research and there are several trials looking into role of prehabilitation as an intervention for improve outcomes in frail patients undergoing surgery.

Another interesting observation was that Fried frailty phenotype showed statistically significant association with physical composite score of QoL while Edmonton frailty score showed strong association with mental composite score of QoL The key to this difference may lie in the way these frailty assessment tools are constructed. Fried frailty phenotype has robust measures of physical strength like gait speed and grip strength in its construct which may make it more sensitive to detect deficiency in physical parameters of QoL. On the other hand Edmonton frailty score additionally records cognitive impairment in form of drawing 'clock face test', which may give it an edge in detecting deficiency in mental parameters of QoL This difference points to the fact that all frailty assessment tools are not made equal and vary in their ability to detect different domains of frailty.

5.3.13 SENSITIVITY AND SPECIFICITY ANALYSIS FOR FRAILTY MEASURES

To determine how sensitive and specific Fried frailty and Edmonton frailty score were in predicting poor QoL in this older population group with CAD, we used the ROC curve

(Receiver Operating Curve). The "Below" and "Far Below" scores in the SF-12 QoL survey were used as surrogate frailty outcomes against which the frailty scores by the two frailty assessment tools were tested. Separate ROC curves were generated for physical composite score (PCS) and mental composite score (MCS) obtained from baseline SF-12 quality of life questionnaire. The cumulative Edmonton frailty score was generate by adding all the individual domain scores together and used as a scale for the analysis. This was done to smoothen the ROC curve. Similarly cumulative Fried frailty score was used to generate the ROC curve.

The ROC curve for the SF-12 physical composite score had fairly acceptable AUC (area under curve) for both the frailty scores tested (Fried frailty score=0.80, Edmonton frailty score=0.77) (Figure 5-10, 5-11). This suggested that both scores can accurately predict a decline in the physical parameters of QoL. Further analysis of the coordinates of the Edmonton frailty score, suggested that a cut-off score value of 3.50 and 4.50 offered a good balance between the sensitivity and specificity. At cut-off score of 3.50 the sensitivity was 78% while the specificity was 58%. At cut-off value 4.50 the sensitivity was 70% while the specificity was 78%. Similarly a cut off score value of 1.50 attained a sensitivity of 70% and specificity of 86%. At cut off of 2.50 there was a marked fall in the estimated sensitivity of Fried frailty phenotype.

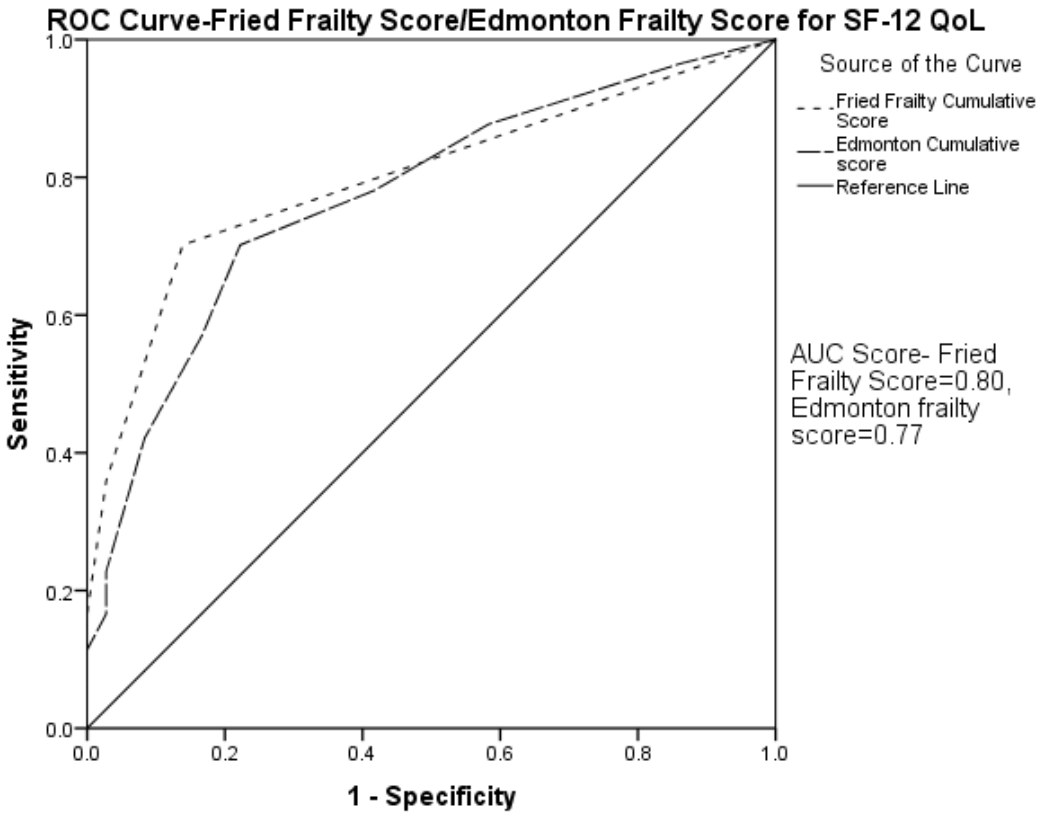


Figure 5-6: ROC curve for Fried frailty phenotype and Edmonton frailty scale measuring for SF-12 Physical composite score quality of life score (SF-12 PCS QoL)

Area Under the Curve- Fried Frailty Score/Edmonton Score for SF-12 Physical Composite Score					
Test Result Variable(s)	**Area under curve**	**Std. Error**	**Asymptotic Significance**	**Asymptotic 95% Confidence Interval**	
				Lower Bound	**Upper Bound**
Fried Frailty Score	0.798	0.038	0.000	0.725	0.872
Edmonton Cumulative score	0.773	0.042	0.000	0.690	0.856

Coordinates of the Curve for SF-12 PCS			
Test Result Variable(s)	**Positive if Greater Than or Equal To[a]**	**Sensitivity**	**1 - Specificity**
Fried Frailty Cumulative Score	-1.00	1.000	1.000
	0.50	0.912	0.750
	1.50	0.702	0.139
	2.50	0.360	0.028
	3.50	0.167	0.000
	4.50	0.026	0.000
	6.00	0.000	0.000
Edmonton Cumulative score	0.00	1.000	1.000
	1.50	0.965	0.861
	2.50	0.877	0.583
	3.50	0.781	0.417
	4.50	0.702	0.222
	5.50	0.570	0.167
	6.50	0.421	0.083
	7.50	0.325	0.056
	8.50	0.228	0.028
	9.50	0.167	0.028
	10.50	0.114	0.000
	11.50	0.070	0.000
	12.50	0.035	0.000
	13.50	0.009	0.000
	15.00	0.000	0.000

The test result variable(s): Fried Frailty Cumulative Score, Edmonton Cumulative score has at least one tie between the positive actual state group and the negative actual state group.
a. The smallest cut off value is the minimum observed test value minus 1, and the largest cut off value is the maximum observed test value plus 1. All the other cut off values are the averages of two consecutive ordered observed test values.

Table 5-12 : Area under the curve and co-ordinates of the curve for Fried frailty phenotype and Edmonton frailty scales for SF-12 PCS QoL

The ROC curve for the SF-12 mental composite score also had fair AUC (area under the curve) values. The AUC value for Edmonton frailty score was 0.74 while the Fried frailty score had a lower value of 0.68. Analysis of the coordinates for Edmonton frailty score showed a sensitivity of 75% and specificity of 62% for a cut-off score value of 5.5. For Fried frailty scale the cut-off score value of 1.50 had sensitivity of 73% but specificity of only 49%. If the cut-off value was increased to 2.50 the sensitivity dropped to 46% and the specificity increased to 78% (Table 5-13)

Both Fried frailty phenotype and Edmonton frailty scale seem to have good sensitivity and specificity to detect poor QoL which has been used as the standard for poor outcome for these frailty measures to detect. None of the two frailty scales have combined sensitivity and specificity above 90% at any cut off score level and hence cannot be the gold standard test to screen for frailty in this older subset of participants with coronary artery disease. This may be impossible to achieve this in practice as frailty often co-exist with comorbidity and disability which can affect the QoL as well.

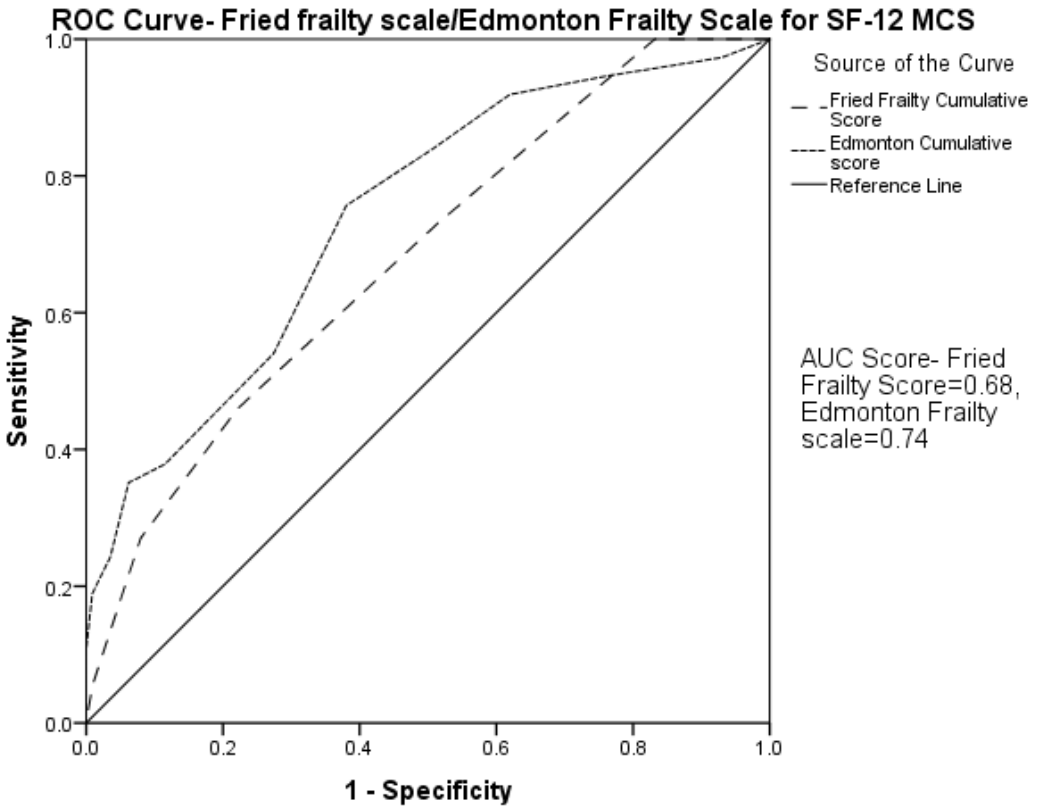


Figure 5-7: ROC curve for Fried frailty phenotype and Edmonton frailty scale measuring for SF-12 mental composite quality of life score (SF-12 MCS QoL)

Area Under the Curve- Fried Frailty scale/Edmonton Score for SF-12 QoL Mental Composite Score					
Test Result Variable(s)	**Area under Curve**	**Std. Error**	**Asymptotic Significance**	**Asymptotic 95% Confidence Interval**	
				Lower Bound	**Upper Bound**
Fried Frailty Score	0.681	0.049	0.001	0.584	0.777
Edmonton Cumulative score	0.739	0.047	0.000	0.648	0.831

Coordinates of the Curve for SF-12 MCS			
Test Result Variable(s)	**Positive if Greater Than or Equal To[a]**	**Sensitivity**	**1 - Specificity**
Fried Frailty Cumulative Score	-1.00	1.000	1.000
	0.50	1.000	0.832
	1.50	0.730	0.513
	2.50	0.459	0.221
	3.50	0.270	0.080
	4.50	0.054	0.009
	6.00	0.000	0.000
Edmonton Cumulative score	0.00	1.000	1.000
	1.50	0.973	0.929
	2.50	0.946	0.761
	3.50	0.919	0.619
	4.50	0.838	0.504
	5.50	0.757	0.381
	6.50	0.541	0.274
	7.50	0.459	0.195
	8.50	0.378	0.115
	9.50	0.351	0.062
	10.50	0.243	0.035
	11.50	0.189	0.009
	12.50	0.108	0.000
	13.50	0.027	0.000
	15.00	0.000	0.000

The test result variable(s): Fried Frailty Cumulative Score, Edmonton Cumulative score has at least one tie between the positive actual state group and the negative actual state group.
a. The smallest cut off value is the minimum observed test value minus 1, and the largest cut off value is the maximum observed test value plus 1. All the other cut off values are the averages of two consecutive ordered observed test values.

Table 5-13 : Area under the curve and co-ordinated for the curve for Fried frailty phenotype and Edmonton frailty score measuring for SF-12 MCS QoL.

5.3.14 CONCORDANCE BETWEEN FRIED FRAILTY PHENOTYPE AND EDMONTON FRAILTY SCORE RESULTS:

To establish whether there was concordance between the Fries frailty phenotype and Edmonton frailty scores of the individual participants we compared their scores (Table 5-14). To assess concordance not-frail were given score of zero while pre-frail or vulnerable were given score of 1 and frail group were scored 2.

Edmonton frailty score	**2**	2 (1.3%)	12 (8%)	25 (16.7%)
	1	1 (0.75)	22 (14.7%)	10 (6.7%)
	0	17 (11.3%)	54 (36%)	7 (4.7%)
		0	**1**	**2**
			Fried frailty score at baseline	

Table 5-14: Comparison between scores measured by Fries frailty phenotype and Edmonton Frailty scores where 0=Not Frail, 1= Pre-frail and 2=Frail

There was concordance between the two frailty scores in 42.7%, with extreme dis-concordance between the results in 6.0%. The commonest discordance occurred in 36% participants whereby the Fried frailty score identified them as pre-frail while Edmonton frailty score marked them as not frail.

5.3.15 DISCUSSION ON CONCORDANCE ANALYSIS RESULTS:

This analysis showed that there was complete concordance or difference of one stage between the frailty measurements in majority of the participants. However, in 9 cases (6%) the frailty results were opposite for the two frailty measures used. Hence, all frailty measures are not created equal. It is important to identify an appropriate frailty measure for a particular population or even a particular purpose and validate it against an accepted standard. The majority of the difference in the measurements was between the pre-frail and the non-frail group. Around 54 (36%) participants were graded as pre-frail by Fried frailty score but were considered not frail by Edmonton frailty score. The reason for this is likely to be the way the way the marking schemes for each frailty tool is constructed. For Fried frailty phenotype, a positive score on even one of the domains or questions is marked as pre-frail while for Edmonton frailty score up to 5 positive scores are still graded as not-frail. Hence the threshold of Fried frailty score for marking participants as pre-frail is much lower compared to Edmonton frailty score.

5.3.16 ANALYSIS OF COHORT BASELINE CHARACTERISTICS AS PER SEX.

During the analysis of the baseline characteristics of the cohort it was noted that the female participants had higher prevalence of frailty compared to the male sex. To explore this further we analysed the cohort characteristics as per their sex. (see table 5-15)

Majority of the demographic and clinical characteristics between the two sexes were well matched. Male participants had significant high incidence of history of previous MI (49.5% vs 31.4%). This can be explained by high incidence of cardiovascular disease in male population compared to female. The female participants had lower creatinine clearance scores compared to males. Although the comorbidity and risk score of the sexes were equally matched it was noted that the number of female patients undergoing CABG surgery were considerably lower than the male participants. This might suggest a selection bias on behalf of the surgeons but this cannot be further explored as number patient undergoing CABG in the cohort is very low. The analysis also suggested that female participants in the study had higher prevalence of frailty and lower physical composite score for QoL. The mental composite scores of QoL were similar across the sexes. This finding needs to be further explored as this difference may be related to lower muscle mass in females hence lower muscle strength. However in our study the difference was picked up both by Fried Frailty score and Edmonton Frailty score suggesting an actual difference. Further research is required to explain this difference. It may be the sex specific frailty scores may need to be developed.

		Cohort Characteristics as per Sex		
		Male (n=99) Mean±SD/%	Female (n=51) Mean±SD/%	P Value
Age		83.5±3.1 (82.9-84.1)	84.0±3.5 (83.1-85.0)	0.30
BMI		27.6±4.8 (26.6-28.5)	26.7±4.4 (25.5-27.9)	0.30
h/o hypertension		69 (69.7%)	33 (64.7%)	0.38
h/o Diabetes mellitus		32 (32.3%)	8 (15.7%)	0.23
h/o previous MI		49 (49.5%)	16 (31.4%)	**0.03**
Creatinine Clearance value		55.9±21.1 (51.7-60.2)	46.2±15.7 (41.8-50.6)	**<0.01**
Charlson's Comorbidity score		6.7±2.0 (6.3-7.1)	6.1±2.6 (5.4-6.9)	0.12
Diagnosis	**Stable Angina**	47 (47.5%)	21 (41.2%)	0.78
	Unstable Angina	11 (11.1%)	5 (9.8%)	
	NSTEMI	27 (27.3%)	18 (35.3%)	
	STEMI	14 (14.1%)	7 (13.7%)	
CCS Angina Class-Baseline	**CCS class I**	14 (14.1%)	8 (15.7%)	0.77
	CCS class II	26 (26.3%)	16 (31.4%)	
	CCS class III	36 (36.4%)	19 (37.3%)	
	CCS class IV	6 (6.1%)	1 (2.0%)	
	No chest pain	17 (17.2%)	7 (13.7%)	
NYHA Class-Baseline	**Class I**	8 (8.1%)	2 (3.9%)	0.46
	Class II	60 (60.6%)	27 (52.9%)	
	Class III	26 (26.3%)	18 (35.3%)	
	Class IV	5 (5.1%)	4 (7.8%)	
Management	**Medical**	53 (53.5%)	31 (60.8%)	0.20
	PCI	33 (33.3%)	18 (35.3%)	
	CABG	13 (13.1%)	2 (3.9%)	
GRACE 1yr mortality		16±17% (13-19%)	14±10% (11-17%)	0.43
EuroScore II		4.6±4.9% (3.7-.6%)	5.6±4.7% (4.3-6.9%)	0.26
Fried Score baseline	**Not Frail**	16 (16.2%)	3 (5.9%)	**0.07**
	Pre-Frail	60 (60.6%)	29 (56.9%)	
	Frail	23 (23.2%)	19 (37.3%)	
Edmonton Score baseline	**Not Frail**	59 (59.6%)	19 (37.3%)	**0.03**
	Vulnerable	22 (22.2%)	11 (21.6%)	
	Mild Frailty	8 (8.1%)	11 (21.6%)	
	Moderate	7 (7.1%)	6 (11.8%)	
	Severe	3 (3.0%)	4 (7.8%)	
SF-12 Physical composite score		38.4±9.6 (36.5-40.3)	34.4±12.4 (30.9-7.9)	**0.03**
SF-12 Mental composite score		52.6±11.2 (50.4-4.9)	50.0±11.2 (46.8-3.2)	0.17

Table 5-15: Cohort characteristics analysis as per sex/gender

5.4 OVERALL DISCUSSION:

In this chapter we showed that,

1) Octogenarian patients with symptomatic CAD are a high risk group for adverse events with multiple comorbidities as suggested by their high Charlson comorbidity, Grace and Euro scores.
2) The prevalence of Frailty in the selected study cohort was 26.1-28.0% measured by Fried frailty phenotype and Edmonton frailty scale. As expected, there was a considerable overlap between frailty, comorbidity and disability at this age. 73.8% of the frail patients in the study had at least one significant comorbidity as well a disability.
3) The Frail participants in the study had higher symptom burden. They had higher prevalence of CCS Angina Class III and IV (66.7 vs 21%) and NYHA Class III and IV symptoms (54.8 vs 42.9%) compared to non-frail participants.
4) Prevalence of frailty was higher among the females compared the male participants in the study.
5) The mental composite scores of the participant group were at par with general population but the physical composite scores were below par in 75% of the participants.
6) Frail participants in the study had significant lower health related QoL compared to non-frail participants. This was reflected in both physical and mental composite scores for QoL.
7) Regression analysis showed that physical parameters of QoL was significantly related to Fried frailty phenotype score while mental composite score for quality of life was significantly related to Edmonton frailty score.
8) At a score of 1.50 Fried Frailty phenotype had 70% sensitivity and 86% specificity for detecting low physical composites of QoL. At the same cut-off Fried frailty score had sensitivity of 73% and specificity of 49% for detecting low mental composites of QoL.
9) For Edmonton Frailty score a cut-off value of 3.5-4.5 had sensitivity of 70% and specificity of 78% for measuring low physical composites of QoL. At score of 5.5 it had sensitivity of 75% and specificity of 62% for detecting low mental composites of QoL.
10) There was full concordance between the Fried frailty score and Edmonton frailty scale in 42.7%. However, the two scores were completely discordant in 6.0%.

Cardiovascular diseases remain the most common cause of mortality in the older adult population worldwide. These patients often have a number of comorbid conditions and live with functional deficits, if not disabilities, in their everyday life. Even when interventions are done to control their symptoms they may not experience any improvement in their QoL because of their co-existing disabilities. American heart association recommends screening older patients with CAD and acute coronary syndromes for frailty, cognitive decline and comorbid conditions and to take these factors into consideration while formulating their management plans(9). There is growing evidence for a strong association between frailty syndrome and cardiovascular disease and QoL. There is high prevalence of frailty in patients with cardiovascular disease and an increased incidence of sub-clinical cardiovascular disease in patients with frailty(137, 185). Studies have also shown a strong association between frailty and poor QoL. There is evidence that QoL improves after coronary intervention primarily due to relief of angina symptoms(186).However, the mean age of the participants in these studies was much less compared to our study cohort. The impact of frailty on QoL is likely to be more enhanced in unselected cohort of older adult patients like in our study.

The prevalence of frailty varies depending upon the frailty measure used and the characteristics of the population. In our study the mean age was 83.7±3.2 years and the prevalence of frailty was around 28% when using Fried frailty phenotype and 26% by using Edmonton frailty scale. In a study with large pooled data of over 61500 community dwelling individuals the prevalence of frailty was 15.7% in age 80-84 years individual and 26.1% in over 85 years old(79). Our study cohort was a mix of both outpatients with stable angina as well as patients admitted with acute coronary syndromes. The proportion of patients with frailty admitted with acute coronary syndromes was much higher (FFP 70% vs EFS 58.3%) suggesting an association between CAD and frailty. In older hospitalised patients with cardiovascular disease there is only limited evidence regarding the prevalence of frailty but has been quoted in range of 27% to 50%(84) . There was also noted that the female participants in the study tend to be frailer compared to their male counterparts (FFP 37.7% vs 23.3%). Hence Females were 1.6 times more likely to be frail than males. This may have been because females tend to have lower average lean body mass and muscle strength. There is always an overlap between frailty, comorbidity and disability. In our analysis this overlap was significantly high (85.7% between frailty, comorbidity and disability) as previously cited in the literature. This is likely because the mean age of our study cohort is much higher

(83.7±3.2) and the setting of study was hospital based rather than community. This is expected, as burden of comorbidity and disability is expected to increase with advance age. The Charlson comorbidity score of frail participants was significantly high. Also the frail participants in the study had a higher CCS angina and NYHA class of symptoms compared to non-frail participants. This may be reflection of the burden of their underlying cardiovascular disease contributing to their frailty.

Many studies have shown a significant correlation between frailty and QoL but again there are only a handful of studies exploring this relation in older adult individuals with coronary artery disease(187). Regression analysis of the cohort data suggested a significant inverse relationship between frailty and QoL. Both physical and mental composite scores of quality of life went down as the frailty scores increased. SF-12 QoL survey form was used in our study. There are studies validating use of SF-12 in elderly cohort but not in this setting(188). This study also proves feasibility of use of SF-12 form in octogenarian patients with coronary artery disease.

We used poor quality of life as a surrogate marker for frailty outcome, and used ROC curves to estimate sensitivity and specificity of Fried frailty phenotype and Edmonton frailty scale. This has not been done before in such a study context. Both frailty scales only achieved acceptable sensitivity and specificity values to be used as screening tools in this group of older patients with coronary artery disease.

5.5 WHAT THIS ANALYSIS ADDS:

1) This study adds to the limited evidence on frailty and QoL in patients above eighty years of age presented to hospital with CAD. There exists a significant negative correlation between frailty and QoL. Our study was different as it was conducted on unselected cohort of patients

2) This study quantifies the degree of overlap between frailty, comorbidity and disability in older adults with symptomatic CAD.

3) It evidences the use of Fried frailty phenotype, Edmonton frailty scale and SF-12 QoL questionnaire in older adult population with coronary artery disease.

4) Fried frailty phenotype and Edmonton frailty scale have acceptable sensitivity and specificity to screen for frailty in this patient group.

6 CHAPTER- SHORT TERM EFFECT OF FRAILTY ON CLINICAL OUTCOMES AND QOL IN OLDER ADULTS WITH CAD- LONGITUDNAL ANALYSIS

6.1 INTRODUCTION:

Cardiovascular disease remains the leading cause of death worldwide. According to WHO, ischemic heart disease caused 144.6 deaths per 100000 population in high income economies in 2015(189). The prevalence of CAD increases with age; It affects 35% of UK males above 80 years of age(1, 190). We have already demonstrated in Chapter 5, in an unselected group of patients aged ≥80yrs with CAD, that frailty is present in 26-28%. Frailty is associated with health related QoL. In this chapter we will explore the longitudinal relationship between these parameters at follow up.

6.2 METHODS:

6.2.1 AIMS:

The main objective of this analysis is to assess participants for change in frailty status and QOL following treatment, and to determine the short term clinical outcome.

6.2.2 STUDY POPULATION:

The structure and protocol for the study has already been described in detail in Chapter 4. All alive patients were invited for a follow-up visit to undergo a repeat assessment of frailty and QoL. To maximize follow up rate participants were offered a home visit if they couldn't attend hospital.

6.2.3 STATISTICAL ANALYSIS:

The statistical analyses were carried out using the IBM SPSS package version 24 with some analysis and graphs made with STATA 14 program. For analysis of follow up data only the participants who attended both baseline and follow up visits were included in the analysis. The missing values and dropout patients were excluded from these analyses. Summary of missing values in the cohort data at follow up is shown in (figure 6-1). Missing data can reduce the statistical power of a study and can produce biased estimates, leading to invalid conclusions. Hence we decided to exclude the missing values altogether. Descriptive statistics of the variables were explored before each sub-analysis. Continuous variable were recorded as mean, median with standard deviation and confidence intervals while categorical variables were recorded as proportions. Paired t- test was used to compare differences in variables at baseline and follow up.

Multiple regression analysis was carried out to determine the effect of various treatments on the frailty status. The statistical significance level was set at 95 % i.e. p value of 0.05. The relationship between baseline frailty and QOL at follow up was explored by doing a simple linear and backward stepwise regression both for physical and mental composite scores of QOL. The assumptions of normality and equal variance were checked. To determine the effect of frailty on survival, Kaplan Meier survival curves were generated. Curves were plotted both for Fried frailty phenotype and Edmonton frailty scores. The difference between the curves was judged with log Rank, Breslow and Tarone-Ware p values. Kaplan Meier survival curves were also plotted for various management strategies. The proportion of complications stratified as per frailty scores and management strategies were compared to look for any significant association.

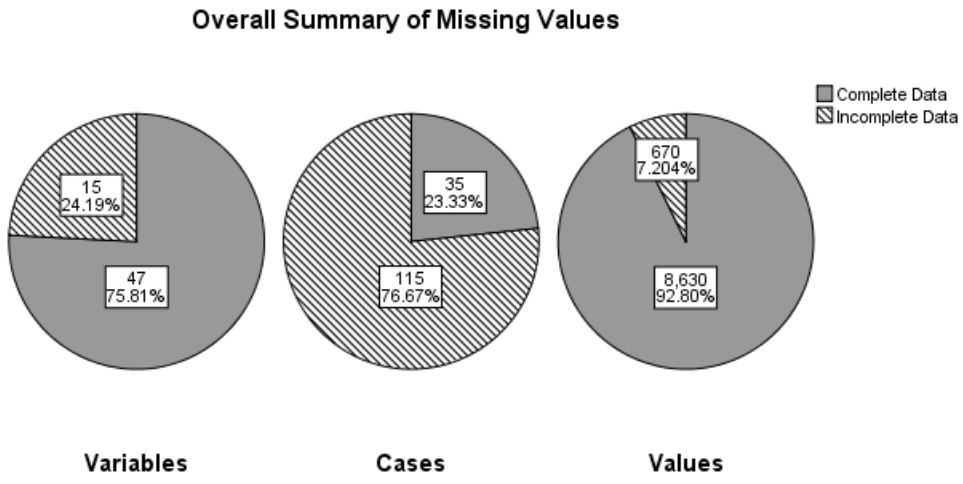


Figure 6-1: Summary of missing values in the cohort data at follow up. Missing values were excluded from analysis

6.3 RESULTS:

6.3.1 CHARACTERISATION OF STUDY COHORT AT FOLLOW UP

Of the total cohort of 150 participants, 103 (68.7%) attended for a follow-up visit at a mean of 114 days after the first visit (table 6-1).

	Baseline		**Follow up (mean=114 days)**
Total study cohort	150	.	.
Deaths before follow up	.	14 (9.3%)	.
Did not attend follow up	.	33 (22%)	.
Total study cohort	.	.	103 (68.7%)

Table 6-1 : Breakdown of participants in the study at first follow-up. The mean day to follow-up was 114 days.

The age specific mortality rates in our study group ranged between 6.5% and 18.2% (Table 6-2).

Age (n=total in age group)	Number of deaths (%)
80-84 yrs (n=93)	6 (6.5%)
85-89 yrs (n=46)	4 (8.7%)
90 yrs and above (n=11)	2 (18.2%)
Gender (n=total in group)	**Number of deaths**
Female (n=51)	7 (13.7%)
Male (n=99)	5 (5.1%)

Table 6-2: Distribution of deaths as per age groups at first follow-up

6.3.2 DISCUSSION ON STUDY COHORT CHARACTERISTICS AT FOLLOW-UP.

As per British Heart Foundation cardiovascular statistics, the age-specific mortality rate from coronary artery disease in 75-84 years old is 12.4%, and over 85 years old it is 10.7%(3). We expect our mortality rate to be higher as the study cohort included hospitalised patients rather than community dwelling mix of healthy individuals. The mortality rate in our study is 9.3% at 114 days which is roughly four months period. The characteristics of the participants that died before follow up are discussed in detail in section 6.3.3.

Loss to follow-up has always been high in studies with older participants because of the higher mortality rate and drop out at follow-up. Our study was no exception, with 22% participants withdrawing from the study following their baseline assessment. Home visits were offered to study participants whenever possible to reduce the loss to follow up. In our pilot study, 21 patients had home visits done. Difficulty to travel to hospital was recognised in majority of study participants as they needed someone to drive them to the appointments in most cases. This point should be kept in mind when planning a large scale study to cater for travel fund for the elderly participants. FFS and EFS are both mixed questionnaire and task based frailty tools. In present scenario, a questionnaire based frailty assessment would offer advantage over task based one as the follow up can be completed remotely or via post.

To characterise the study cohort at the first follow up and to explore the effects of their respective treatments, the approach of excluding the cases which did not attend follow up, was taken. Analysis of the deaths in the study was carried out with respect to their baseline variables, to help identify any significant predictor of their adverse outcome.

As the study is exploratory in nature and not powered for detecting significant predictors for discrete endpoint we decided against imputing missing values.

6.3.3 COMPARISON OF ALIVE STUDY PARTICIPANTS WITH LOSS TO FOLLOW UP AND DEATHS:

Comparison was made to determine any differences between participants who remained in the study and participants that were lost to follow up or died (table 6.3)

Characteristics of Alive Study participants vs Deaths and loss to follow-up					
		Alive (n=103)	**Death (n=14)**	**Loss at followup (n=33)**	**p-value**
Age		83.6 (83-84)	85.7 (83-89)	82.9 (82-84)	0.018
Male		70 (68%)	7 (50%)	22 (66.7%)	0.411
BMI		27.33±0.39 (26.54-28.11)	26.34±1.45 (23.22-29.47)	27.48±1.08 (25.29-29.67)	0.732
h/o hypertension		65 (63.1%)	10 (71.4%)	27 (81.8%)	0.128
h/o Diabetes Mellitus		25 (24.3%)	5 (35.7%)	10 (30.3%)	0.574
Diagnosis	**SA**	29 (47.6%)	1 (7.1%)	18 (54.5%)	0.045
	USA	13 (12.6%)	1 (7.1%)	2 (6.1%)	
	NSTEMI	29 (28.2%)	8 (57.1%)	8 (24.4%)	
	STEMI	12 (11.7%)	4 (18.6%)	5 (15.2%)	
CCS Angina Class-Baseline	**No angina**	6 (5.8%)	2 (14.3%)	2 (12.1%)	0.137
	Class I	14 (13.6%)	0 (0.0%)	5 (15.2%)	
	Class II	33 (32%)	1 (7.1%)	7 (21.2%)	
	Class III	34 (33%)	5 (35.7%)	11 (33.3%)	
	Class IV	16 (15.5%)	6 (42.9%)	6 (18.2%)	
NYHA Class-Baseline	**Class I**	6 (5.8%)	2 (14.3%)	2 (6.1%)	0.009
	Class II	64 (62.1%)	4 (18.6%)	19 (57.6%)	
	Class III	29 (28.2%)	4 (18.6%)	11 (33.3%)	
	Class IV	4 (3.9%)	4 (18.6%)	1 (3.03%)	
ECG-SR/AF	**SR**	89 (86.4%)	12 (85.7%)	25 (75.8%)	0.342
	AF	14 (13.6%)	2 (14.3%)	8 (24.2%)	
ECHO		n=78	n=12	n=24	
Normal LV function		42 (53.8%)	1 (8.3%)	13 (54.2%)	
Mild LV function		18 (23.08%)	3 (25.0%)	5 (20.8%)	
Mod to severe LV		18 (23.08%)	8 (66.7%)	6 (25.0%)	
Management Strategy	**Medical**	57 (55.4%)	8 (57.1%)	19 (57.6%)	0.541
	PCI	36 (35.0%)	6 (42.9%)	9 (27.3%)	
	CABG	10 (9.7%)	0 (0.0%)	5 (15.2%)	
Charlson's Comorbidity score		6.34±0.21 (5.9-6.6)	8.1±0.8 (6.4-9.9)	6.4±0.36 (5.8-7.2)	0.014
GRACE 1yr mortality		13.62±1.3% (11.1-16.2%)	30.49±6.9% (15.5-45.4%)	13.49±1.6% (10.3-16.7%)	0.001
Fried Score baseline	**Not Frail**	13 (12.6%)	2 (14.3%)	4 (12.1%)	0.377
	Pre-Frail	63 (61.2%)	5 (35.7%)	21 (63.6%)	
	Frail	27 (26.2%)	7 (50%)	8 (24.2%)	
Edmonton Score baseline	**Not Frail**	61 (59.2%)	3 (21.4%)	14 (42.45)	0.059
	Vulnerable	17 (16.5%)	6 (42.9%)	10 (30.3%)	
	Mild Frail	14 (13.6%)	1 (7.2%)	4 (12.1%)	
	Moderate	8 (7.8%)	3 (21.4%)	2 (6.1%)	
	Severe	3 (2.9%)	1 (7.2%)	3 (9.1%)	
SF-12 PCS score baseline		37.55±1.10 (35.4-39.7)	36.04±2.61 (30.4-41.7)	36.04±1.74 (32.5-39.6)	0.729
SF-12 MCS score baseline		52.65±1.13 (50.4-54.9)	47.88±2.56 (42.4-53.4)	50.56±1.91 (46.7-54.5)	0.263

Table 6-3: Comparison of Deaths in the study with alive participants and patients lost to follow up. Data is presented as n (%) or for continuous variables mean (95% confidence intervals).

6.3.4 DISCUSSION ON COMPARISON OF ALIVE, LOSS TO FOLLOW-UP AND DEMISED PARTICIPANTS:

This comparison was essential before any further analysis on the remaining study participants was carried out. One of the aim of this comparison, was to assess whether participants who were lost at follow up were frailer than those who attended for a follow up visit. Table 6-3 shows that these two groups are comparable in their frailty characteristics. As the number of deaths in the study were small in number (n=14) it was impossible to conduct any complex statistical analysis. This analysis was done as an exploration comparing the proportions and means of participants who were alive at follow up with those who had died and those who did not attend the follow up. The mean age of the participants that died was higher than those alive, and had a significantly higher Charlson's comorbidity score (8.1 vs 6.3). As expected, deaths were in higher proportion in patients presenting with acute myocardial infarction, STEMI and NSTEMI combined.

6.3.5 COMPARISON OF STUDY COHORT AT FOLLOW-UP WITH BASELINE. (SHORT TERM EFFECTS)

Detailed breakdown of the basic characteristics of the study cohort at follow up is shown in Table 6-4. It includes participants that attended the follow up hence the total number is reduced from 150 to 103. Their clinical characteristics were compared to determine the effect their treatments had on them.

Characteristics comparison at Baseline (n=103) and follow up		Mean±SD/(%)
Age		83.6±3.0 (83.0-84.1)
Male		70 (68.0%)
Female		33 (32.0%)
BMI		27.3±4.0 (26.5-28.1)
h/o hypertension		64 (62.1%)
h/o Diabetes mellitus		25 (24.8%)
h/o previous MI		46 (44.7%)
h/o previous PCI		42 (40.8%)
h/o CABG		11 (10.7%)
h/o Device implantation		6 (5.8%)
h/o Heart Failure		10 (9.7%)
Creatinine Clearance grade	**eGFR>85**	7 (6.8%)
	eGFR 50-85	45 (43.7%)
	eGFR<50	50 (48.5%)
	On dialysis	0 (0.0%)
Charlson's Comorbidity score		6.4±2.1 (6.0-6.8)
GRACE 1yr mortality		13.6±13.0% (11.1-16.2)
Diagnosis	**Angina**	48 (46.6%)
	Unstable Angina	14 (13.6%)
	NSTEMI	29 (28.2%)
	STEMI	12 (11.7%)
ECG	**Sinus Rhythm**	89 (86.4%)
	Atrial Fibrillation/Flutter	14 (13.6%)
LV function	**Normal LV**	43 (54.4%)
	Mildly impaired	18 (22.8%)
	Moderately impaired	13 (16.5%)
	Severely impaired	5 (6.3%)

Table 6-4: Basic characteristics of patients in study at follow up

Characteristics comparison at Baseline and follow up		Baseline (n=103) Mean±SD/(%)	At follow up (n=103) Mean±SD/(%)	p-value
CCS Angina Class	**No chest pain**	7 (6.8%)	61 (59.2%)	0.00
	CCS class I	15 (14.6%)	17 (16.5%)	
	CCS class II	33 (32.0%)	20 (19.4%)	
	CCS class III	32 (31.1%)	5 (4.9%)	
	CCS class IV	16 (15.5%)	0 (0.0%)	
NYHA Class	**NYHA Class I**	6 (5.8%)	17 (16.5%)	0.05
	NYHA Class II	64 (62.1%)	55 (53.4%)	
	NYHA Class III	29 (28.2%)	27 (26.2%)	
	NYHA Class IV	4 (3.9%)	4 (3.9%)	

Table 6-5: CCS angina and NYHA Class of patients at follow up

Similarly the frailty characteristics and quality of life parameters of the study cohort were compared to baseline to determine the effect different managements strategies may have had on the study participants (table 6-7, 6-8, and 6-9).

Comparison of frailty scores and QoL parameters at Baseline and follow-up				
		Baseline (n=103) Mean±SD/(%)	**At follow up (n=103) Mean±SD/(%)**	**p-value**
Fried Frailty Phenotype	**Not Frail**	13 (12.6%)	19 (18.5%)	0.56
	Pre-Frail	62 (60.2%)	54 (52.4%)	
	Frail	28 (27.2%)	30 (29.1%)	
Edmonton Frailty Score	**Not Frail**	60 (58.3%)	60 (58.3%)	0.66
	Vulnerable	17 (16.5%)	19 (18.4%)	
	Mild Frailty	15 (14.6%)	16 (15.5%)	
	Moderate Frailty	8 (7.8%)	4 (3.9%)	
	Severe Frailty	3 (2.9%)	4 (3.9%)	
SF-12 PCS score		37.2±11.0 (35.1-39.4)	38.5±11.3 (36.3-40.7)	0.27
SF-12 MCS score		52.7±11.5 (50.4-54.9)	55.1±10.6 (53.0-57.2)	0.04
Physical health composite score	**At or above**	27 (26.2%)	33 (32.0%)	0.19
	Below	13 (12.6%)	13 (12.6%)	
	Far below	63 (61.2%)	56 (54.4%)	
Mental health composite score	**At or above**	81 (78.6%)	84 (81.6%)	0.19
	Below	4 (3.9%)	7 (6.8%)	
	Far below	18 (17.5%)	11 (10.7%)	

Table 6-6: Table showing frailty and quality of life scores at baseline and follow up. Participants who did not attend follow up were excluded from the analysis.

6.3.6 DISCUSSION ON BASIC CHARACTERISTICS OF COHORT AT FOLLOW-UP:

Comparison of the baseline and follow up characteristics of the participants showed a significant improvement in their symptoms at follow up. The participants who did not report any chest pain at follow up increased from 12.6% to 59.2%. Similarly a trend towards decreasing CCS angina class of symptoms was noted across the cohort. However, there wasn't much change seen in the NYHA class of the participants. The only significant shift in NYHA class was from NYHA class II to I. This suggests that the treatments received by these participants made some improvement in their shortness of breath but a marked difference to their angina symptoms.

Another observation to note was that there wasn't any significant difference between the frailty scores and physical composite score for QoL scores at follow up compared

with their baseline. There was improvement in mental composite score for QoL which may be a reflection of improvement in their symptoms and wellbeing after treatment. There was no change in frailty status at all, suggesting that the treatments participants received for their coronary artery disease did not make any significant difference to their frailty status. Despite decreasing angina symptoms, it did not translate into improvement in frailty scores. This may be due interaction with comorbid condition and disability. The only sub-group that seemed to benefit from these treatments was the pre-frail sub-group. This may indicate a degree of reversibility in frailty when comorbid condition is treated.

There was no difference between the mean SF-12 physical composite score at follow up (37.2±11 vs 38.5±11.3, p=0.27) while the SF-12 mental composite score showed evidence of significant improvement (52.7±11.5 vs 55.1±10.6, p=0.04). From these findings we can infer that the treatment these participants received did not significantly improve physical measures of QoL but did make difference to their mental composite scores. This is most likely due to improvement in their symptoms rather than their physical capabilities. Although, statistically significant different but whether it translate into any meaningful clinical improvement needs to be determined as the frailty parameters did not significantly change. Another explanation of this change might be that the baseline MCS values of the participants may have been low due to their illness and now returned to normal after treatments. Without control groups this will be hard to ascertain with the present data.

6.3.7 EFFECT OF MANAGEMENT STRATEGIES ON FRAILTY AND QUALITY OF LIFE PARAMETERS

To explore the effects of different management strategies on the study cohort, sub-analyses of the cohort according to the treatments they received was carried out. Mean Frailty and QoL parameters of the groups undergoing various management strategies were compared at baseline and at follow up. Figure 6-1 and 6-2 gives a holistic picture of the effect of respective treatments on the frailty and quality of life parameters.

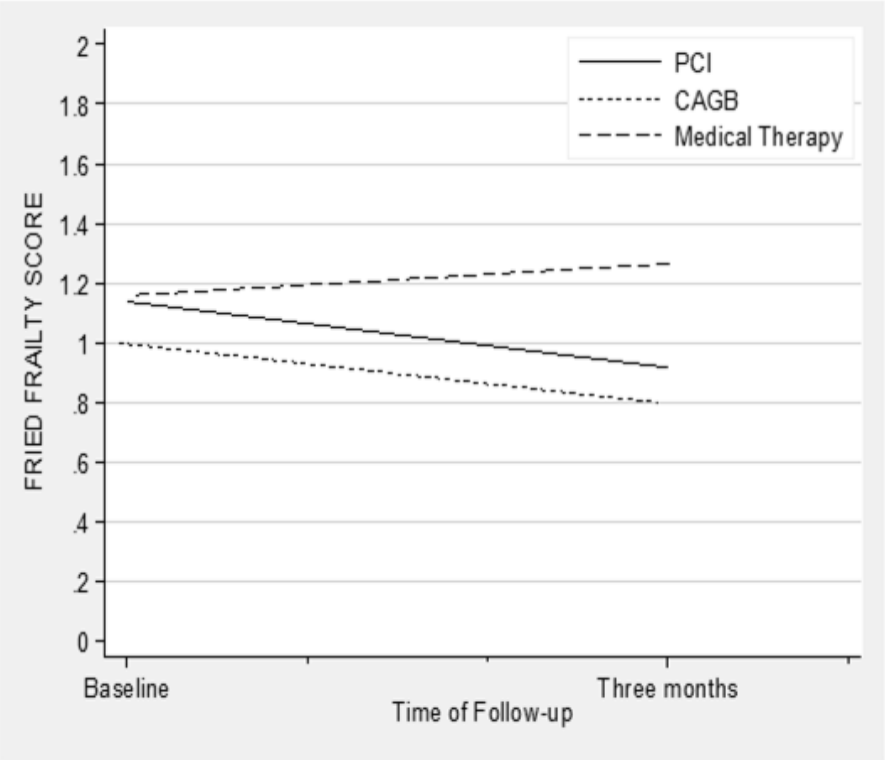
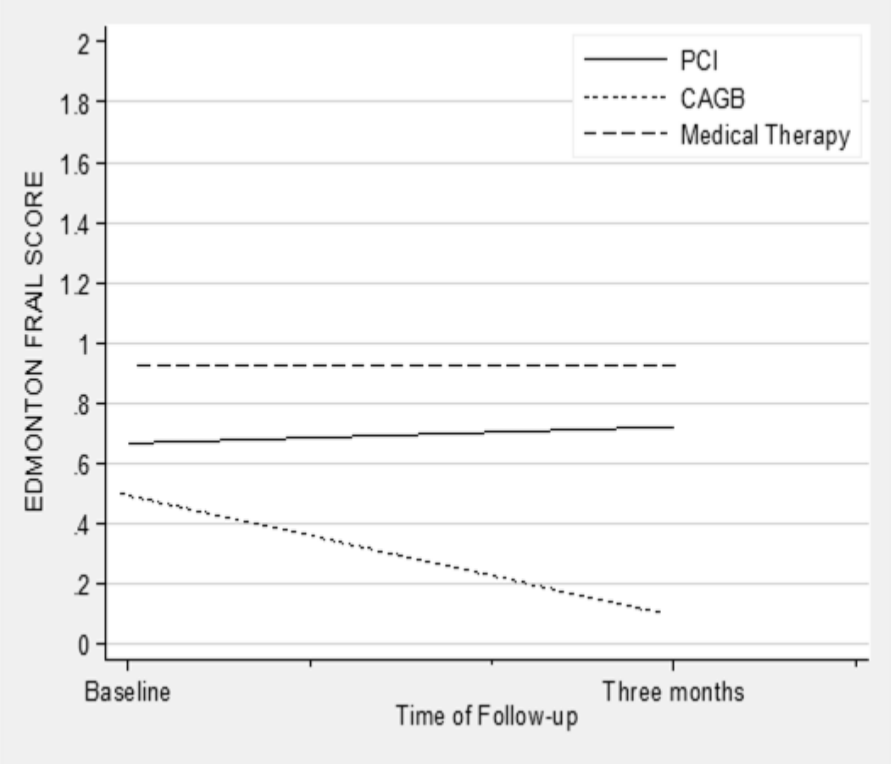


Figure 6-2: Graph showing trend of mean frailty scores in the cohort at follow up as per the treatment received by the participants.



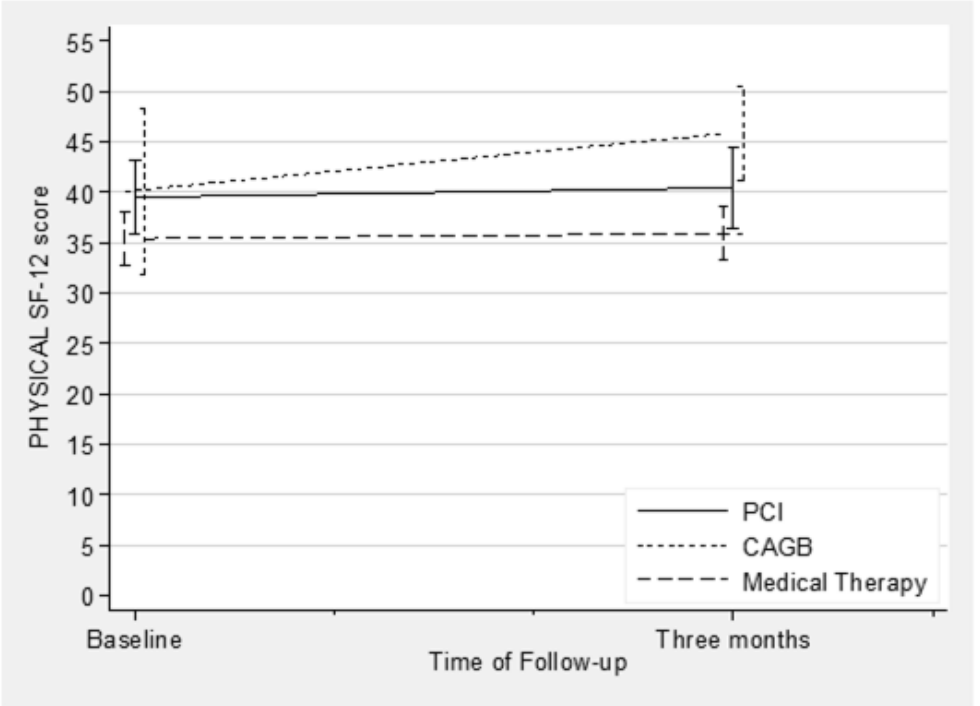
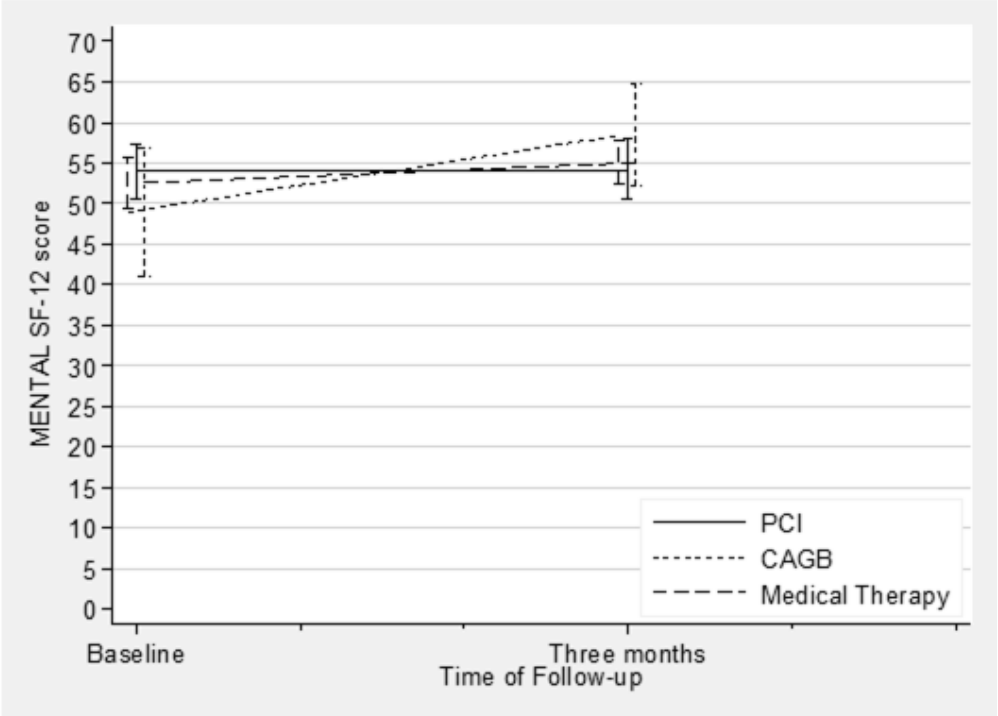


Figure 6-3: Graph showing trend of mean SF-12 physical composite score and SF-12 mental composite score as per the treatments received by the participants.



The graphs (figure 6-2, 6-3) suggested some improvement in frailty and QoL parameters with percutaneous coronary intervention and CABG surgery however in medically managed patients these parameters stayed the same. To explore in details the effect of these management strategies had on the participants undertaking them, we compared their clinical characteristics at baseline and follow up. The effect of medical management are tabulated in table 6-7.

		Management-Medical (n=57)		
		Baseline	**Follow up**	**P value**
Age		83.9±3.2 (83.0-84.7)		
Male		36 (63.2%)		
Female		21 (36.8%)		
Diagnosis	**Angina**	39 (68.4%)		
	Unstable Angina	8 (14.0%)		
	NSTEMI	9 (15.8%)		
	STEMI	1 (1.8%)		
CCS Angina Class	**No Chest Pain**	2 (3.5%)	27 (47.4%)	**0.00**
	Class I	13 (22.8%)	11 (19.3%)	
	Class II	24 (42.1%)	14 (24.6%)	
	Class III	17 (29.8%)	5 (8.8%)	
	Class IV	1 (1.8%)	0 (0.0%)	
NYHA Class	**Class I**	3 (5.3%)	3 (5.3%)	0.17
	Class II	31 (54.4%)	35 (61.4%)	
	Class III	21 (36.8%)	18 (31.6%)	
	Class IV	2 (3.5%)	1 (1.8%)	
Fried Frailty Score	**Not Frail**	6 (10.5%)	5 (8.8%)	0.24
	Pre-Frail	35 (61.4%)	31 (54.4%)	
	Frail	16 (28.1%)	21 (36.8%)	
Edmonton frailty Score	**Not Frail**	32 (56.1%)	32 (56.1%)	0.79
	Vulnerable	7 (12.3%)	10 (17.5%)	
	Mild Frailty	10 (17.5%)	7 (12.3%)	
	Moderate Frailty	5 (8.8%)	4 (7.0%)	
	Severe Frailty	3 (5.3%)	4 (7.0%)	
SF-12 PCS score		35.3±10.2 (32.5-38.0)	35.9±10.4 (33.1-38.6)	0.71
SF-12 MCS score		52.5±11.9 (49.4-55.7)	55.1±10.1 (52.4-57.8)	**0.07**

Table 6-7: Table showing effect of medical management on symptoms, frailty status and quality of life at follow up

The effect of PCI management strategy on the clinical characteristics, frailty and quality of life parameters are described in table 6-8.

		Management-PCI (n=36)		
		Baseline	**Follow up**	**p-value**
Age		83.6±3.0 (82.5-84.6) (82.5-84.6)		
Male		26 (72.2%)		
Female		10 (27.8%)		
Diagnosis	**Angina**	8 (22.2%)		
	Unstable Angina	4 (11.1%)		
	NSTEMI	13 (36.1%)		
	STEMI	11 (30.6%)		
CCS Angina Class	**No Chest Pain**	3 (8.3%)	25 (69.4%)	0.00
	Class I	2 (5.6%)	5 (13.9%)	
	Class II	7 (19.4%)	6 (16.7%)	
	Class III	9 (25.0%)	0 (0.0%)	
	Class IV	15 (41.7%)	0 (0.0%)	
NYHA Class	**Class I**	2 (5.6%)	12 (33.3%)	0.25
	Class II	26 (72.2%)	13 (36.1%)	
	Class III	6 (16.7%)	8 (22.2%)	
	Class IV	2 (5.6%)	3 (8.3%)	
Fried Frailty Score	**Not Frail**	6 (16.7%)	11 (30.6%)	0.07
	Pre-Frail	19 (52.8%)	17 (47.2%)	
	Frail	11 (30.6%)	8 (22.2%)	
Edmonton frailty Score	**Not Frail**	21 (58.3%)	19 (52.8%)	0.66
	Vulnerable	8 (22.2%)	8 (22.2%)	
	Mild Frailty	5 (13.9%)	9 (25.0%)	
	Moderate Frailty	2 (5.6%)	0 (0.0%)	
	Severe Frailty	0 (0.0%)	0 (0.0%)	
SF-12 PCS score		39.6±11.3 (35.7-43.4)	40.5±12.4 (36.3-44.7)	0.66
SF-12 MCS score		53.9±10.5 (50.4-57.5)	54.2±11.5 (50.3-58.1)	0.91

Table 6-8: Table showing the effect of percutaneous coronary intervention on the symptoms, frailty status and quality of life at follow up.

The patients undergoing CABG surgery formed a very small proportion of the cohort. There characteristics were also explored in a similar way as the other groups in Table 6-9.

		Management-CABG (n=10)		
		Baseline	**Follow up**	**p-value**
Age		82.1±1.8 (80.8-83.4)		
Male		8 (80%)		
Female		2 (20%)		
Diagnosis	**Angina**	1 (10%)		
	Unstable Angina	2 (20%)		
	NSTEMI	7 (70%)		
	STEMI	0 (0.0%)		
CCS Angina Class	**No Chest Pain**	2 (20%)	9 (90%)	0.00
	Class I	0 (0.0%)	1 (10%)	
	Class II	2 (20%)	0 (0.0%)	
	Class III	6 (60%)	0 (0.0%)	
	Class IV	0 (0.0%)	0 (0.0%)	
NYHA Class	**Class I**	1 (10%)	2 (20%)	0.34
	Class II	7 (70%)	7 (70%)	
	Class III	2 (20%)	1 (10%)	
	Class IV	0 (0.0%)	0 (0.0%)	
Fried Frailty Score	**Not Frail**	1 (10%)	3 (30%)	0.17
	Pre-Frail	8 (80%)	6 (60%)	
	Frail	1 (10%)	1 (10%)	
Edmonton frailty Score	**Not Frail**	7 (70%)	9 (90%)	0.27
	Vulnerable	2 (20%)	1 (10%)	
	Mild Frailty	0 (0.0%)	0 (0.0%)	
	Moderate Frailty	1 (10%)	0 (0.0%)	
	Severe Frailty	0 (0.0%)	0 (0.0%)	
SF-12 PCS score		40.1±13.2 (30.7-49.6)	45.9±7.5 (40.5-51.2)	0.11
SF-12 MCS score		49.0±12.8 (39.8-58.1)	58.4±10.0 (51.3-65.6)	0.07

Table 6-9: Table showing effect of CABG surgery on symptoms, frailty status and quality of life at follow up.

To further explore and quantify change in frailty levels within the treatment subgroups, we categorised the changes in frailty scores as seen in Table 6-10. The change in the frailty scores were calculated to identify where this change was happening.

Change (Follow up - Baseline scores)	PCI (n=36)	CABG (n=10)	Medical therapy (n=57)	Total (n=103)
Fried Frailty Phenotype				
-2	1 (2.8%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
-1	10 (27.8%)	2 (20%)	9 (15.8%)	21 (20.4%)
0	22 (61.1%)	8 (80%)	34 (59.6%)	64 (62.1%)
1	2 (5.6%)	0 (0.0%)	13 (22.8%)	15 (14.6%)
2	1 (2.8%)	0 (0.0%)	1 (1.8%)	2 (1.9%)
Edmonton Frailty Score				
-3	0 (0.0%)	1 (10%)	0 (0.0%)	1 (1.0%)
-2	0 (0.0%)	0 (0.0%)	6 (10.5%)	6 (5.8%)
-1	7 (19.4%)	2 (20%)	6 (10.5%)	15 (14.6%)
0	22 (61.1%)	6 (60%)	33 (57.9%)	61 (59.2%)
1	5 (13.9%)	1 (10%)	8 (14.0%)	14 (13.6%)
2	2 (5.6%)	0 (0.0%)	4 (7.0%)	6 (5.8%)

Table 6-10: Table showing change in frailty scores at follow up stratified as per treatment received

To ascertain the strength of this impact of management strategies on frailty a binary logistic regression was carried out keeping fried frailty phenotype score at follow up as the outcome indicator, see table 6-11.

Fried Frailty Phenotype at Follow up	Binary Logistic Regression (Nagelkerke R^2=0.35) (Hosmer Lemeshow Test=0.16)			Backward Stepwise Regression (Nagelkerke R^2=0.34) (Hosmer Lemeshow Test=0.85)		
	β±SE	p value	OR	β±SE	p value	OR
Age	0.17±0.09	0.06	1.18 (0.99-1.41)	0.18±0.09	0.04	1.20 (1.01-1.42)
Male	2.12±0.59	0.00	8.29 (2.63-26.19)	2.07±0.58	0.00	7.93 (2.57-24.47)
BMI	0.002±0.07	0.99	1.00 (0.88-1.15)			
h/o hypertension	0.26±0.58	0.65	1.30 (0.42-4.09)			
h/o Diabetes Mellitus	-0.51±0.71	0.47	0.60 (0.15-2.41)	-0.32±0.65	0.62	0.73 (0.20-2.59)
Charlson's Comorbidity score	0.36±0.15	0.01	1.44 (1.08-1.92)	0.36±0.14	0.01	1.44 (1.10-1.89)
Diagnosis						
Stable Angina	0.00					
Unstable Angina	-0.48±1.08	0.66	0.62 (0.08-5.16)			
NSTEMI	-0.89±1.24	0.47	0.41 (0.04-4.65)			
STEMI	-0.31±1.02	0.76	0.73 (0.10-5.42)			
Management Medical Therapy	0.00			0.00		
PCI	-0.75±0.71	0.29	0.47 (0.12-1.87)	-0.55±0.56	0.32	0.58 (0.20-1.72)
CABG	-1.18±1.26	0.35	0.31 (0.03-3.62)	-1.06±1.15	0.35	0.34 (0.04-3.24)

Table 6-11: Binary Logistic Regression and Backward Stepwise regression to show relationship between various treatments on Frailty. Fried Frailty Phenotype at follow up was used as dependant variable.

6.3.8 DISCUSSION ON EFFECT OF MANAGEMENT STRATEGY ON FRAILTY AND QUALITY OF LIFE PARAMETERS:

It seems that all the management strategies including medical therapy, percutaneous intervention and CABG surgery made a significance improvement in participants CCS angina class. This result should be interpreted with caution as patients with STEMI were given CCS class 4 meaning that any treatment would likely to result in improvement in symptoms. Although the difference in NYHA Class did attain significance as a whole, but it was hard to determine from the sub-analysis which treatments contributed significantly to this change. Similarly the sub-analysis of the

SF-12 mental composite score did not help determine, which treatments contributed most to the significance achieved while analysing the cohort as a whole. None of the treatments received by the participants made any significant difference to the frailty status or the physical composites of quality of life of the cohort individually.

Comparison of the frailty scores showed that the mean frailty scores of participants treated medically for their CAD did not get any worse at the follow up .However there was a trend noted towards improvement in mean frailty scores in participants treated with percutaneous intervention and CABG. This trend did not achieve statistical significance as already stated. Majority of the participants present in the study at follow up maintained their baseline frailty level and showed no change with treatments they received (change 0: 62.1% by FFP, 59.2% by EFS). There were only a small group whose frailty scores improved by score of 1 after the treatments at follow up (change -1: 20.4% by FFS,14.6% by EFS).There were only a minority of participants who showed any marked change in their frailty scores from baseline (change ±2: 2.9% by FFP, 5.8% by EFS).

Similarly when mean comparing physical and mental composite scores of QoL at follow up, treatment with improved the QoL score the most. Again this did not attain any statistical significance as the number undergoing CABG low (n=10). Participants who were treated medically and with percutaneous intervention maintained their mean QoL at follow up (Fig 6-3). A lack of any significant relationship between the different management strategies and frailty status at follow up also suggests that their frailty is not an outcome of their underlying disease condition.

Significant improvement in symptoms with various treatments, without a significant change in physical composites of QoL parameters, suggest that the main benefit of these treatment in this age group might be for improvement of symptoms. There was a trend towards improvement noted in these parameters and it may be that in a larger cohort study this trend may gain statistical significance.

6.3.9 RELATIONSHIP BETWEEN BASELINE FRAILTY STATUS AND QUALITY OF LIFE PARAMETERS AT FOLLOW UP

Analysis of the baseline parameters showed a strong relationship between frailty and QoL (Chapter 5). Whether, the relationship persisted at follow up after participants had received their therapies, multiple variable regression was carried out. Further backward stepwise regression model was made to identify the variables most predictive of the variation in QoL. The analysis was carried out both for physical composite score and mental composite scores of QoL. This analysis was done to identify baseline characteristics which would predict quality of life at follow up. (Table 6-12). Multiple variate regression analysis to determine significant predictors for SF-12 mental composite score for QoL at follow up is shown in Table 6-13.

Figure 6-4 and 6-5 shows the inverse relationship between frailty and health related quality of life in a graphical form.

SF-12 PCS score Follow up	Multiple Linear regression (Adj R^2=0.46)		Backward Stepwise Regression (Adj R^2=0.50)	
	β (CI)	p	β(CI)	p
Age	-0.50(-1.16,0.17)	0.14		
Female	-3.98(-8.41,0.46)	0.08	-4.19(-7.82,-0.57)	0.02
BMI	-0.24(-0.73,0.26)	0.34		
h/o hypertension	1.84(-2.10,5.78)	0.36		
h/o Diabetes	-0.37(-4.99,4.26)	0.88		
h/o previous MI	2.90(-2.80,8.61)	0.31		
h/o previous PCI	0.27(-5.06,5.60)	0.92		
CCS Angina Class-Follow up				
No angina	0.00	0.88		
Class I	0.41(-4.69,5.50)			
Class II	0.80(-4.47,6.07)			
Class III	-2.98(-11.99,6.02)			
Class IV				
NYHA Class- Follow up				
Class I	0.00	0.00		
Class II	-6.43(-12.05,-0.80)		-6.58(-11.33,-1.82)	0.01
Class III	-15.78(-22.94,-8.6)		-16.82(-22,35,-11.30)	0.00
Class IV	-23.59(-36.85,-10.33)		-22.66(-33.22,-12.10)	0.00
Charlson's Comorbidity score	-0.86(-9.06,2.50)	0.20		
GRACE 1yr mortality	0.19(-0.04,0.42)	0.10	0.14(-0.01,0.28)	0.07
EUROscore2	0.11(-0.63,0.84)	0.76		
Diagnosis				
Stable Angina	0.00	0.31		
Unstable Angina	-3.28(-9.06,2.50)			
NSTEMI	2.85(-2.45,8.16)			
STEMI	3.78(-5.46,13.02)			
Management				
Medical Therapy	0.00	0.45		
PCI	-1.33(-6.51,3.86)			
CABG	3.04(-3.88,9.95)			
Fried Score baseline				
Non-Frail	0.00	0.07		0.02
Pre-Frail	-6.59(-12.49,-0.69)		-6.28(-11.79,-0.77)	
Frail	-8.40(-15.82,-0.97)		-9.33(-15.63,-3.05)	
Edmonton frailty score baseline				
Non-Frail	0.00	0.71		
Vulnerable	0.95(-4.30,6.20)			
Mild Frailty	-4.00(-10.48,2.47)			
Moderate Frailty	0.59(-6.56,7.73)			
Severe Frailty	-2.25(-16.57,12.08)			

Table 6-12: Multiple variable regression and stepwise backward regression showing relation between Frailty and SF-12 physical composite score at follow up.

SF-12 MCS score Follow up	Multiple Linear regression (Adj R^2=0.01)		Backward Stepwise Regression (Adj R^2=0.039)	
	β±SE	p	β±SE	p
Age	0.12(-0.73,0.97)	0.78		
Female	-1.84(-7.49,3.81)	0.52		
BMI	-0.06(-0.69,0.56)	0.84		
h/o hypertension	-2.93(-7.95,2.09)	0.25		
h/o Diabetes Mellitus	-3.19(-9.08,2.70)	0.28		
h/o previous MI	1.59(-5.68,8.86)	0.66		
h/o previous PCI	2.40(-4.39,9.20)	0.48		
CCS Angina Class-Follow up				
No angina	0.00			
Class I	-1.92(-8.42,4.57)	0.56		
Class II	-2.04(-8.76,4.69)	0.55		
Class III	-1.59(-13.07,9.90)	0.78		
Class IV				
NYHA Class- Follow up				
Class I	0.00			
Class II	3.73(-3.45,10.90)	0.30		
Class III	2.85(-6.29,11.98)	0.54		
Class IV	-2.56(-19.47,14.34)	0.76		
Charlson's Comorbidity score	-1.15(-2.83,0.53)	0.17		
GRACE 1yr mortality	0.05(-0.24,0.33)	0.75		
EUROscore2	0.81(-0.12,1.74)	0.09		
Diagnosis				
Stable Angina	0.00			
Unstable Angina	0.61(-6.76,7.98)	0.87		
NSTEMI	0.13(-6.63,6.90)	0.97		
STEMI	-8.43(-20.21,3.35)	0.16		
Management				
Medical Therapy	0.00			
PCI	1.09(-5.52,7.70)	0.74		
CABG	1.78(-7.04,10.60)	0.69		
Fried Frailty Score baseline				
Non-Frail	0.00			
Pre-Frail	4.25(-3.27,11.78)	0.26		
Frail	4.71(-4.76,14.19)	0.33		
Edmonton frailty score baseline				
Non-Frail	0.00	0.09	0.00	0.07
Vulnerable	-5.92(-12.62,0.78)	0.08	-4.79(-10.40,0.83)	0.09
Mild Frailty	-5.81(-14.07.2.45)	0.17	-3.99(-10.05,2.08)	0.20
Moderate Frailty	-4.63(-13.75,4.48)	0.32	-2.63(-10.32,5.06)	0.50
Severe Frailty	-21.78(-40.05,-3.50)	0.02	-15.2(-27.3,-3.14)	0.01

Table 6-13: Multiple variable regression and backward stepwise regression showing relation between predictor variables and SF-12 mental composite score at follow up.

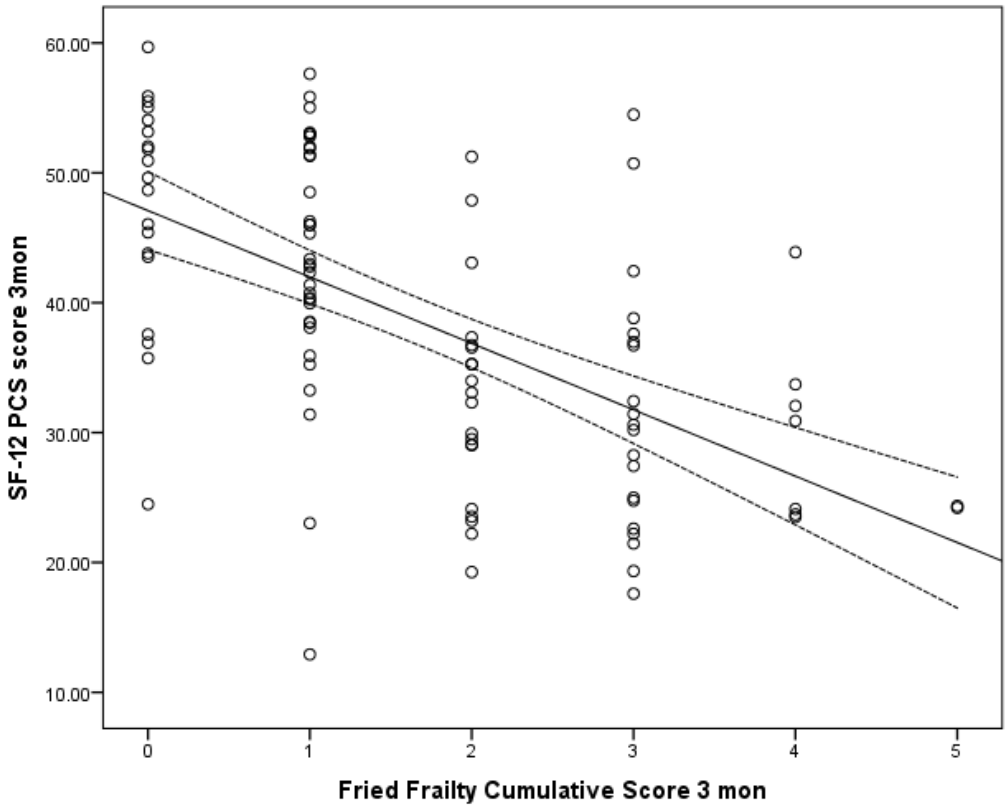
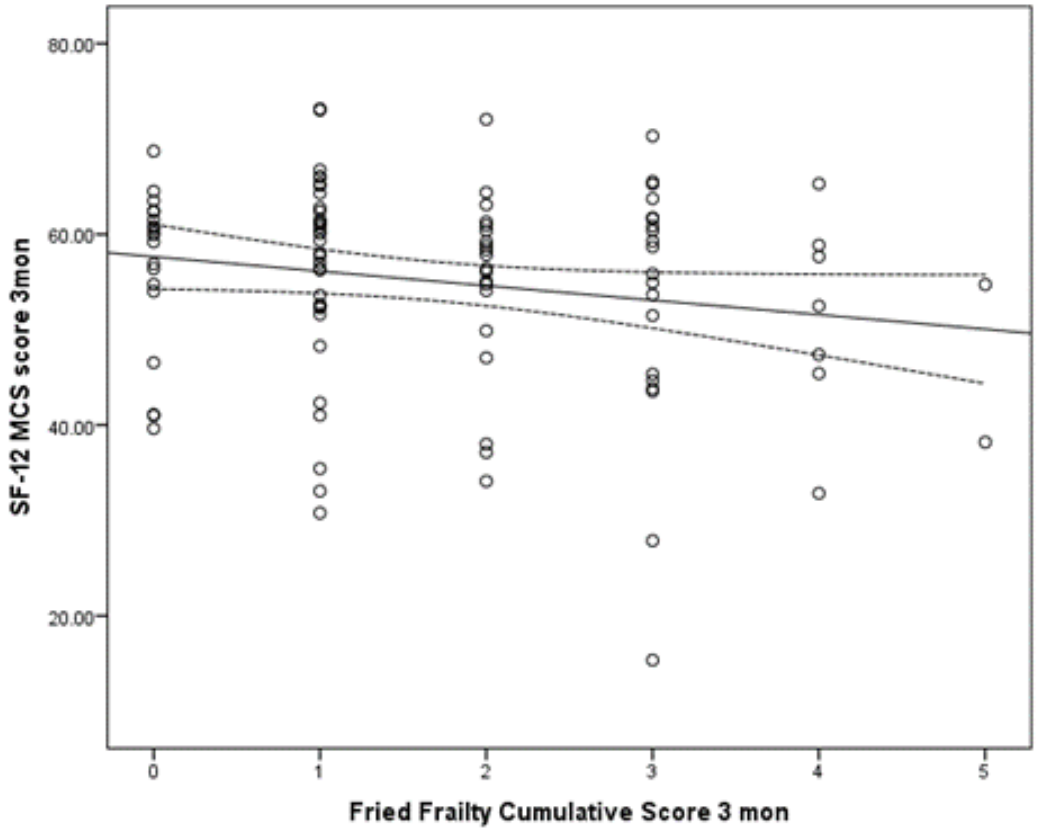


Figure 6-4: Graph showing inverse relationship between Fried frailty phenotype and quality of life parameters.



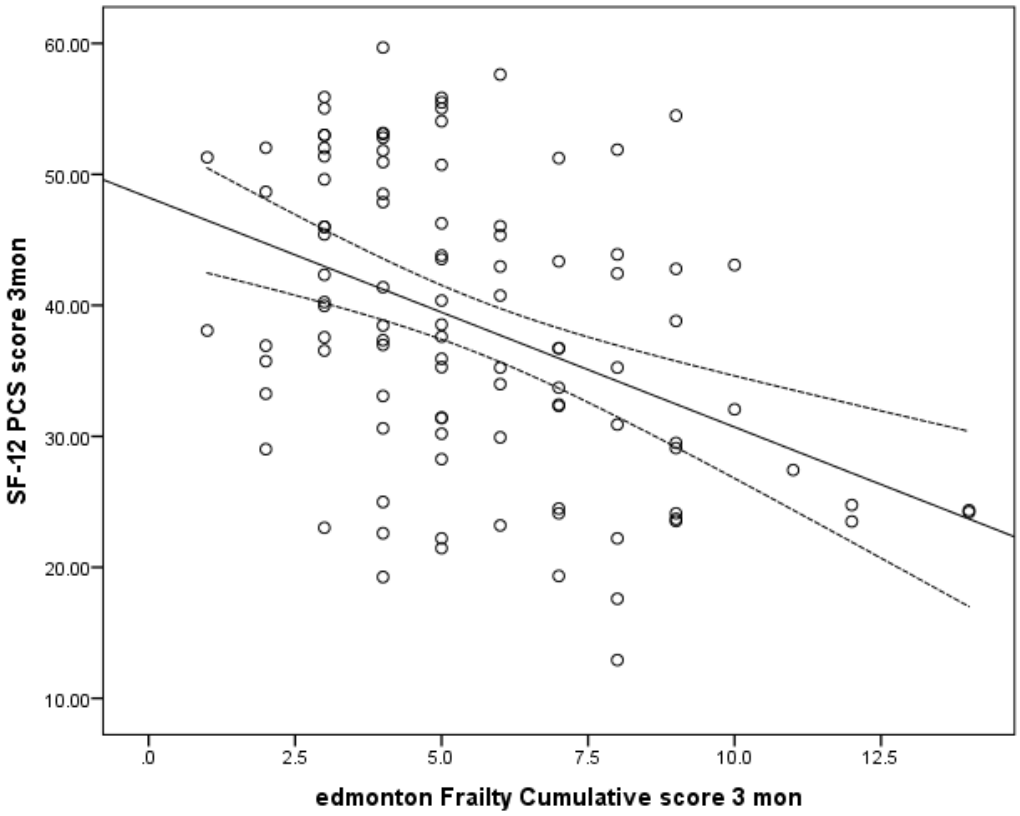
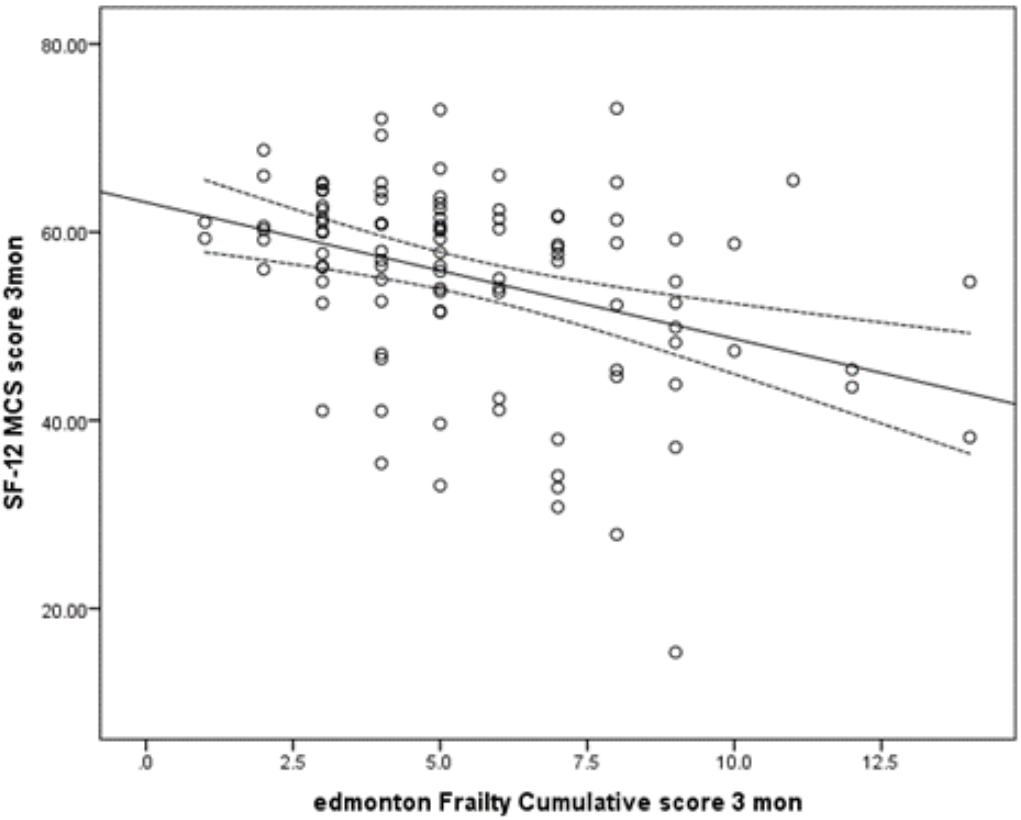


Figure 6-5: Graph showing inverse relationship between Edmonton frailty score and quality of life parameters.



6.3.10 DISCUSSION ON PREDICTORS OFQUALITY OF LIFE AT FOLLOW UP AND IT'S ASSOCIATION WITH BASELINE FRAILTY:

Regression analysis for predictor variables of physical composite score of QoL at follow up showed a significant relationship between Fried frailty phenotype score and SF-12 PCS score ($p<0.05$). This association was also seen at analysis done at baseline. The coefficient for this association suggests an inverse relation between frailty and QoL (Table 6-12). Hence it can be postulated that in older adult patients with CAD any measures to improve frailty is like to improve the physical domain of their QoL down the line. Interestingly, Edmonton frailty scores did not predict this association at follow up analysis while at baseline data analysis there was a strong association seen between Edmonton frailty score and SF-12 PCS QoL . There could be several explanations for this. The follow up analysis was only carried out patients who attended the follow up and patients who did not attend the follow up were excluded. This reduced sample size may have altered the distribution in a way for Edmonton Frailty scores to lose its predictive value. The Edmonton frailty scoring system further subdivides the frail population into groups with mild, moderate and severe frailty. This breakdown left very low numbers in some of the subgroups which can affect the analysis.

On backward stepwise regression analysis, Fried frailty phenotype score at baseline retained its significance as a predictor for quality of life. Similarly baseline NYHA Class of symptoms showed a significant inverse association with physical composite scores of QoL, at follow up. These variables along with sex included in the stepwise regression model explained the variation in the data maximally with adjusted R square value of 0.50. The assumptions of normality and equal variance were met for this regression analysis.

Regression analysis to determine predictors of mental composite score for QoL at follow up revealed quite different results. The analysis included only participants attending the follow up . The adjusted R value for the model was low around 0.09, meaning the analysis model couldn't reliably explain the variation in the data. Hence any generalization of the result should be with caution. The simple linear and stepwise regression analysis showed that Edmonton frailty score at baseline was the only significant predictor of mental composite score of QoL at follow up. This was in contrast to the previous analysis for the physical composite score at follow up where Fried frailty phenotype was a significant predictor of outcome compared to Edmonton

frailty score. It seems that Fried frailty score is better at predicting the physical domains of QoL while the Edmonton frailty scale excels in predicting the mental domains of QoL. The explanation for this may lay in the way these frailty assessment tools are constructed. The Edmonton frailty scale uses clock face construction to assess cognition in addition to other questions about mood to assess the mental domains of quality of life. This may give Edmonton frailty scale edge over other frailty scales to assess mental domains of frailty as well as quality of life. Fried frailty phenotype uses gait speed, grip strength as well as leisure time physical activity questionnaire to assess physical domains of frailty giving it an edge to predict physical domains of QoL.

6.3.11 CHARACTERISATION OF DEATHS IN THE STUDY DURING FOLLOW UP PERIOD

There were 14 deaths in the study cohort before the first follow up. The mean follow up time was 107±39.6 (3-144) days. The days to death was taken as 'follow up time' for participants who died before their follow up. To characterize the deaths in the study participants, variable characteristics were first compared to the participants alive in the study (table 6-16) and Kaplan-Meier survival curves and Cox regression model were used to explore the effect of frailty and various managements on their outcome.

Characteristics of Deaths in Study Cohort at Follow up				
		Deaths (n=14) Mean+SD/ %	**Alive (n=136) Mean+SD/ %**	**p value**
Age		85.7±4.9 (82.9-88.5)	83.4±2.9 (82.9-83.9)	**0.01**
Male		7 (50%)	92 (67.6%)	0.18
Female		7 (50%)	44 (32.4%)	0.18
BMI		26.3±5.4 (23.2-29.5)	27.4±4.6 (26.6-28.1)	
h/o previous MI		7 (50%)	58 (42.6%)	0.59
h/o hypertension		10 (71.4%)	92 (67.6%)	0.77
h/o Diabetes mellitus		5 (35.7%)	35 (25.7%)	0.12
CCS Angina Class-Baseline	No Chest pain	2 (14.3%)	10 (7.3%)	**0.02**
	CCS class I	0 (0.0%)	19 (14.0%)	
	CCS class II	1 (7.1%)	40 (29.4%)	
	CCS class III	5 (35.7%)	45 (33.1%)	
	CCS class IV	6 (42.9%)	22 (16.2%)	
NYHA Class-Baseline	NYHA Class I	2 (14.3%)	8 (5.9%)	**0.001**
	NYHA Class II	4 (28.6%)	83 (61.0%)	
	NYHA Class III	4 (28.6%)	40 (29.4%)	
	NYHA Class IV	4 (28.6%)	5 (3.7%)	
ECG	Sinus Rhythm	12 (85.7%)	114 (83.8%)	0.85

Characteristics of Deaths in Study Cohort at Follow up				
		Deaths (n=14) Mean+SD/ %	**Alive (n=136) Mean+SD/ %**	**p value**
	Atrial Fib/flutter	2 (14.3%)	22 (16.2%)	
	ST depression	2 (14.3%)	16 (11.8%)	0.89
	T wave inversion	3 (21.4%)	24 (17.6%)	
	ST elevation	4 (28.6%)	15 (11.0%)	**0.06**
	LBBB	7 (7.1%)	12 (8.8%)	0.57
	RBBB	2 (14.3%)	9 (6.6%)	
LV Function	Normal	1 (8.3%)	55 (53.9%)	0.003
	Mild LV dysfunction	3 (25.0%)	23 (22.5%)	0.85
	Moderate LV dysfunction	2 (16.7%)	18 (17.6%)	0.93
	Severe LV dysfunction	6 (50.0%)	6 (5.9%)	**0.000**
Diagnosis	Angina	1 (7.1%)	67 (49.3%)	0.003
	Unstable Angina	1 (7.1%)	15 (11.0%)	0.654
	NSTEMI	8 (57.1%)	37 (27.2%)	**0.02**
	STEMI	4 (28.6%)	17 (12.5%)	0.10
GRACE 1yr mortality		30.5±25.9% (15.5-45.4)	13.6±12.1% (11.5-15.6)	**0.00**
Operative risk as per EUROscore2		10.0±7.4% (5.7-14.3)	4.4±4.2% (3.7-5.2)	**0.00**
Management	Medical	8 (57.1%)	76 (55.9%)	0.93
	PCI	6 (42.9%)	45 (33.1%)	0.46
	CABG	0 (0.0%)	15 (11.0%)	0.05
Fried Score baseline	Not Frail	2 (14.3%)	17 (12.5%)	0.13
	Pre-Frail	5 (35.7%)	84 (61.8%)	
	Frail	7 (50.0%)	35 (25.7%)	
Edmonton Score baseline	Not Frail	3 (21.4%)	75 (55.1%)	**0.05**
	Vulnerable	6 (42.9%)	27 (19.8%)	
	Mild Frailty	1 (7.1%)	18 (13.2%)	
	Moderate Frailty	3 (21.5%)	10 (7.4%)	
	Severe Frailty	1 (7.1%)	6 (4.4%)	
SF-12 PCS score baseline		36.0±9.8 (30.4-41.7)	37.2±10.9 (35.3-39.0)	0.65
SF-12 MCS score baseline		47.9±9.6 (42.4-53.4)	52.1±11.4 (50.2-54.1)	0.17
SF-12 PCS score baseline	At or above	2 (14.3%)	34 (25%)	0.64
	Below	2 (14.3%)	14 (10.3%)	
	Far below	10 (71.4%)	88 (64.7%)	
SF-12 MCS score baseline	At or above	10 (71.4%)	103 (75.7%)	0.93
	Below	1 (7.1%)	9 (6.6%)	
	Far below	3 (21.4%)	24 (17.6%)	

Table 6-14: Comparison of characteristics of death in the study cohort before their follow up.

6.3.12 DISCUSSION ON CLINICAL CHARACTERISTICS OF DEATH IN STUDY AT FOLLOW UP:

Analysis of the study variable of deaths in the study helped characterize this high risk group. The deaths in the study were older and had high risk characteristics. Unfortunately there was no access to determine the official cause of the deaths in the study, hence it was hard to ascertain whether they were all cardiovascular deaths. The mean age of the participants was higher for the participants that had died before there follow up (85.7±4.9 vs 83.4±2.9). Comparing the proportional percentages, the participants that died seemed to have higher angina CCS and NYHA class. This may reflect a higher burden of underlying CAD. However, most deaths were observed in the participants presenting with NSTEMI and STEMI, confirming the high risk nature of their underlying disease. This was also indicated in their predicted higher GRACE 1 year mortality risk (30.5% vs 13.6%) and EUROScore II operative risk scores (10% vs 4.4%). Both of these risk assessment tools were able to accurately predict the higher risk participants in the study. There were no deaths in the small group (n=10) who underwent CABG surgery. This is likely because these patients are a preselected group who have already been risk stratified before being accepted to undergo CABG surgery. Besides the surgery group the deaths were slightly higher in medically managed participant compared to those who underwent percutaneous intervention (PCI) (42.9% vs 57.1%).

Patients with heart failure were excluded from the study. There was increased proportion of severe LV dysfunction noted within the group that died (50% vs 5.9%). These were the participants who developed heart failure during the course of the study.

As the number of deaths in the study were very few it was impossible to derive predictors of death from binary regression analysis due to large number sub-group variables not having any figure. To determine the impact of Frailty, our variable of interest, we carried out a limited cox regression and Kaplan-Meier survival curve.

6.3.13 IMPACT OF FRAILTY STATUS ON SURVIVAL

To explore the effect of frailty on the survival/mortality in the study cohort, Kaplan-Meier curve for Fried frailty phenotype and Edmonton frailty score were studied. The

Kaplan-Meier survival curve in subgroups of frailty as per Fried frailty phenotype is

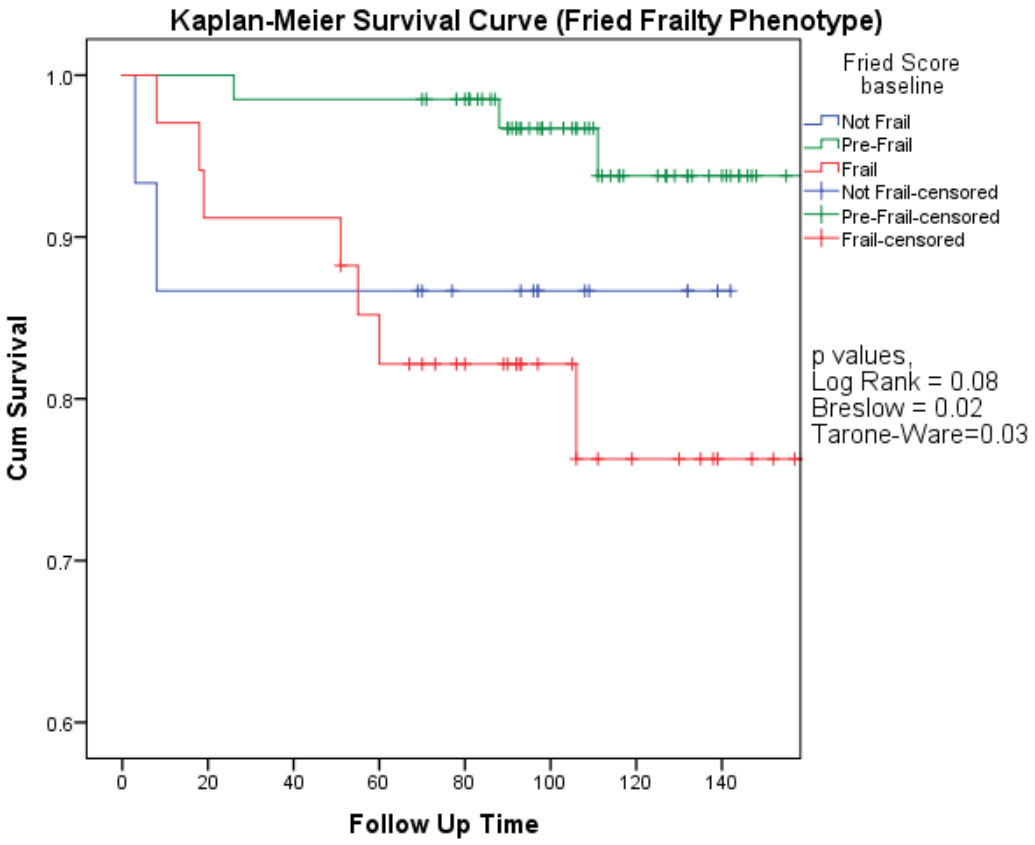


Figure 6-6: Kaplan-Meier curve showing effect of frailty on survival as per Fried frailty phenotype.

shown in figure 6-5 .

The Kaplan-Meier survival curve stratified according to the frailty status as per Fried frailty status has a log rank p-value of 0.08, Breslow p-value of 0.02 and Tarone-Ware p-value of 0.03. The Breslow and Tarone-Ware p values show that there is a significant difference between the survival curve during the initial and mid-range of the survival curve. However Log rank p-value of 0.08 suggest that the difference between the survival curve towards end of the follow up period is not significant. This can be visualised on the graph as the curves have crossed each other towards the end of the follow-up.

The Kaplan-Meier survival curve for frailty subgroups as devised by Edmonton frailty scale is shown in figure 6-6

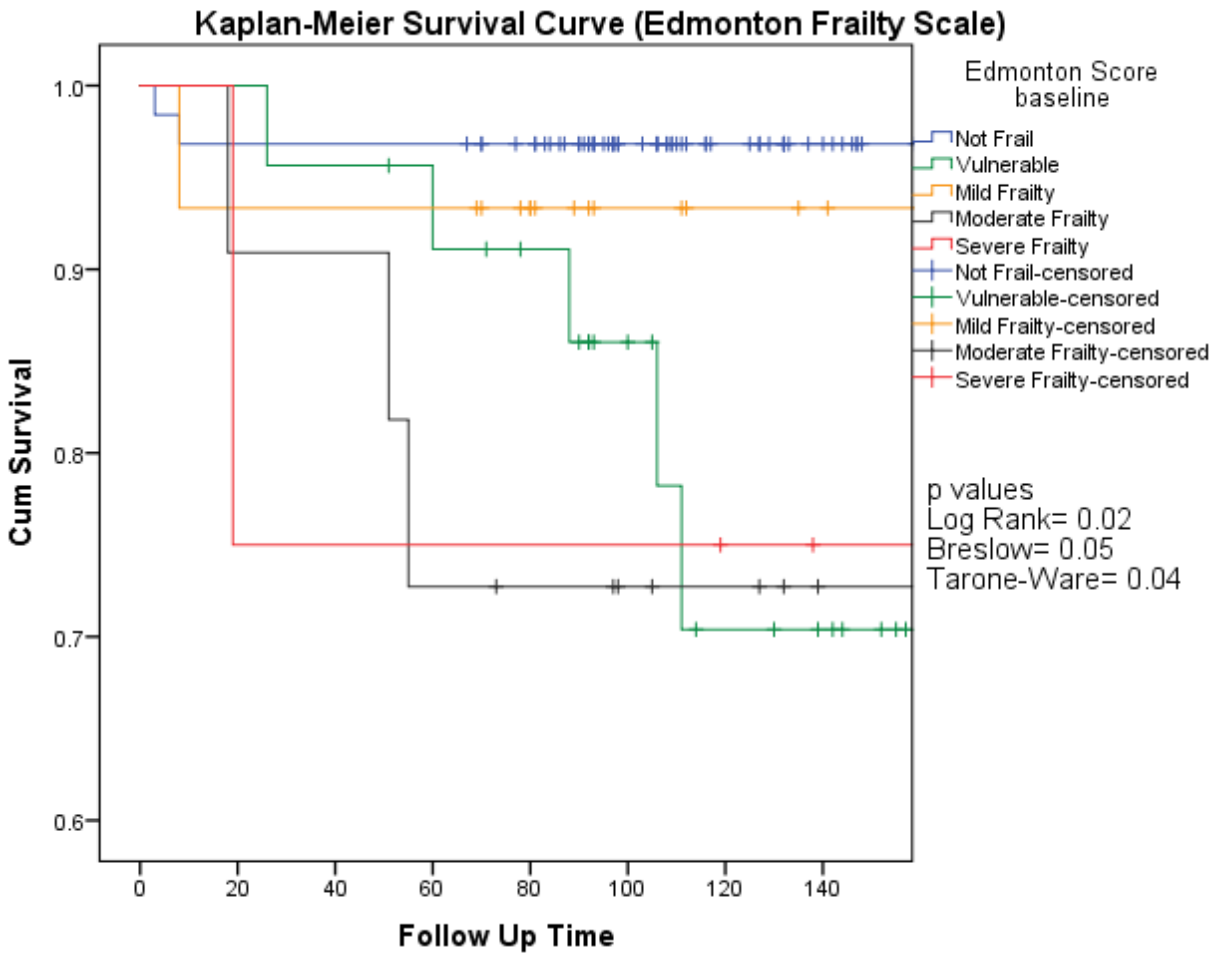


Figure 6-7: Kaplan-Meier curve showing effect of frailty on survival as per Edmonton frailty score.

The log rank p-value for survival curve for Edmonton frailty score was 0.02 while the Breslow and the Tarone-Ware p-value were 0.05 and 0.04 respectively. This suggests that the survival curve stay significantly different throughout the course of follow up period. Furthermore we compared the survival curves of patients undergoing different management strategy to explore any significant association. The Kaplan-Meier survival curve plot as per the management strategy of the participants is shown in figure 6-7.

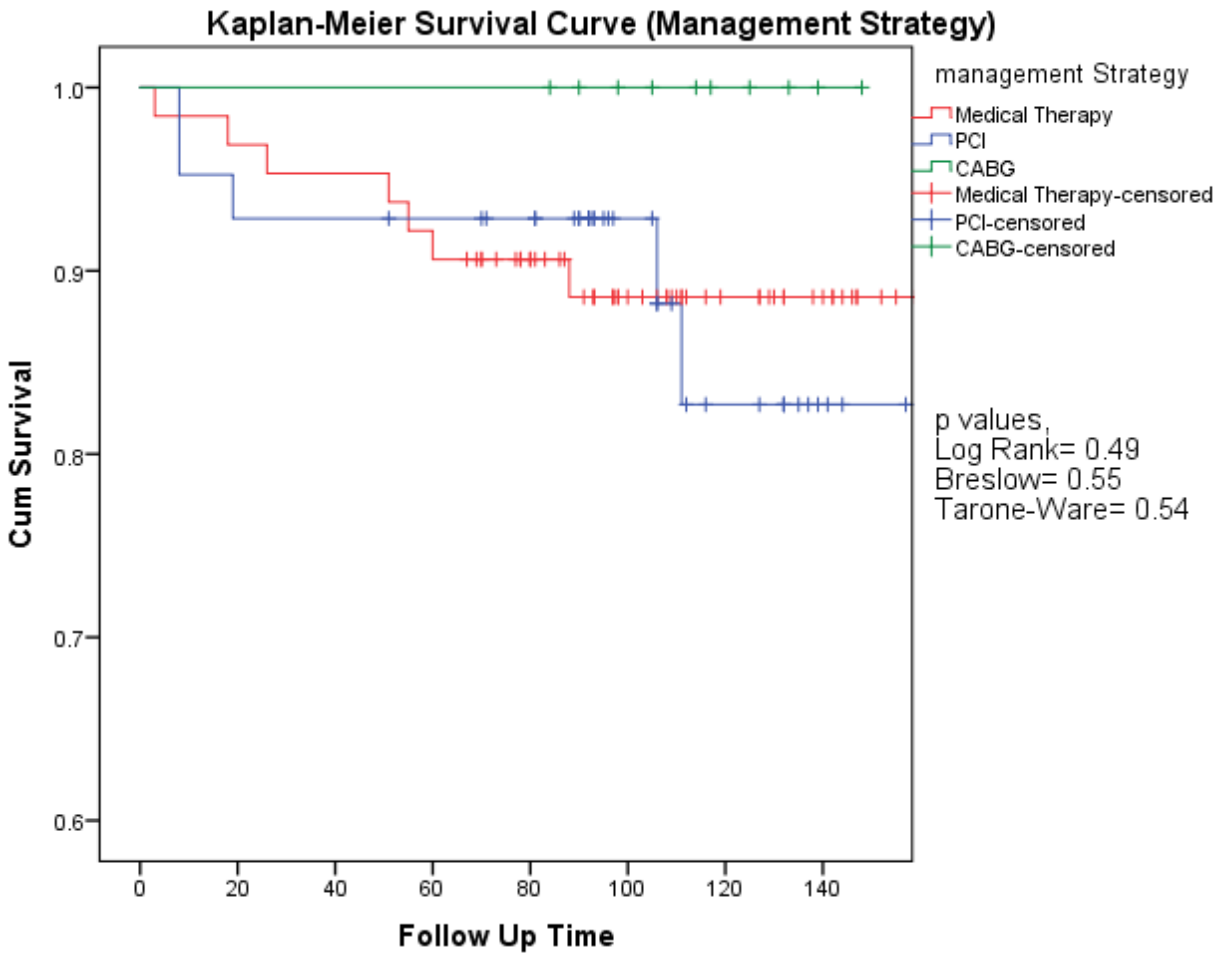


Figure 6-8: Kaplan-Meier curve showing effect of various management strategies on survival

The Log rank, Breslow and Tarone-Ware values were not significantly different for the management strategy survival curves.

6.3.14 DISCUSSION ON KAPLAN-MEIER SUVIVAL CURVES OF FRAILTY SUBGROUPS:

Both the survival analysis indicated that the frail participants had worse survival rates compared to participants who were not frail. This held true for both Fried frailty phenotype as well as Edmonton frailty score. Another observation was that, the survival curve for the pre-frail participants fell below the frail participants' survival curve towards the end (Figure 6-6). This suggests that the pre-frail group of participants may have similar long term risk as the frail group of participants. Similar trend is seen in Kaplan-Meier survival curve stratified according to Edmonton frailty score (Figure 6-7). Also, towards the end of the follow up time period the pre-frail or

the vulnerable group did worse than the frail group. This was an interesting observation and needs further exploring. It may suggest that in the long term the pre-frail or the vulnerable group will perform adversely as the frail group. Hence they should also be considered high risk and managed in a similar way as their frail counterparts. They should be targeted with frailty interventions just as frail population would be. This finding needs to be further established and explored on a larger scale study.

To determine any effect of different management strategies on the survival of the participants, a Kaplan-Meier survival curve stratified according to the treatments received was performed (Figure 6-8). There was no significant difference between the curves throughout its course. Hence, treatment strategies of medical therapy and percutaneous intervention don't seem to offer any significant survival benefit over other. Furthermore it seems like the survival curve for percutaneous intervention seems to be worse than for those managed with medical treatment. This can be explained by the fact that the percutaneous intervention group comprised of high risk patient admitted with NSTEMI and STEMI while the group managed medically comprised predominantly of patients diagnosed with stable angina. Hence, no opinion should be formed about benefit of any particular management strategy from this analysis.

The mortality also seems to increase with increase in the degree of frailty. When comparing the number of deaths according to the increasing scores on the Fried frailty phenotype, increasing proportions of deaths were observed (Fig: 6-8, 6-9). This helps further visualises the relationship between mortality and frailty.

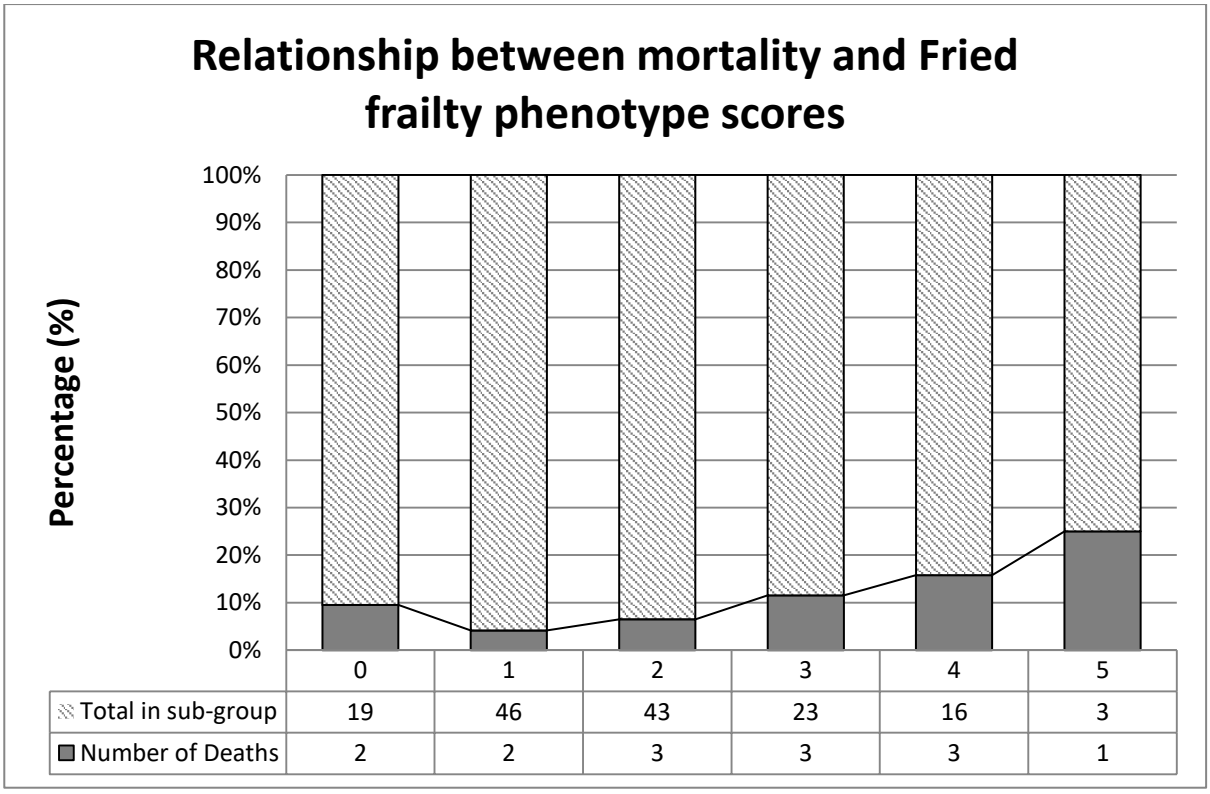


Figure 6-9: Graph showing increasing proportion of mortality with increasing frailty scores.

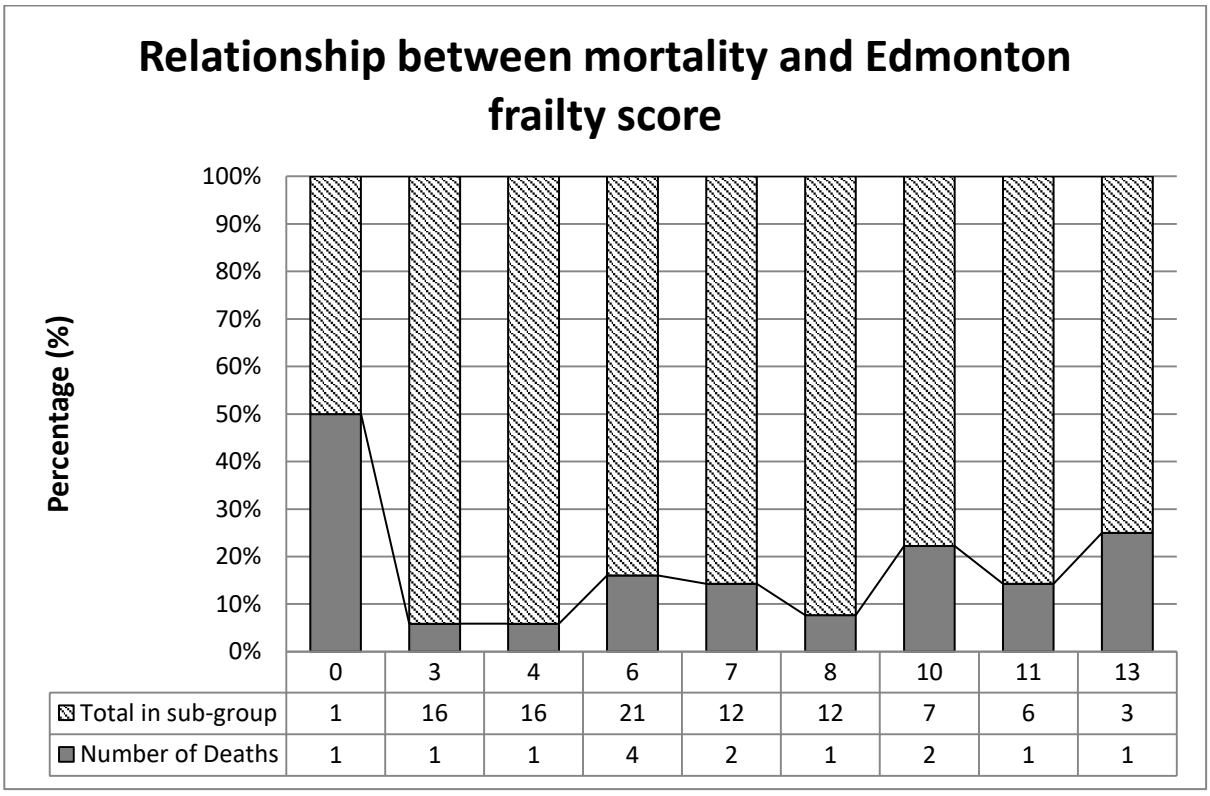


Figure 6-10: Graph showing increasing proportion of mortality with increasing Edmonton frailty scores.

To explore the relationship of participants underlying diagnosis and frailty status on their survival a limited cox regression analysis was carried out. The results of this has to be interpreted and generalised with caution as the number of deaths (n=14) were very low number for statistical analysis. Some of the variables were excluded from the analysis due to no outcome event in the subgroups. Table 6-15 shows that participants underlying diagnosis and Edmonton frailty score at baseline are significantly related to survival.

Cox Hazard Regression (log likelihood= 86.19) (p =0.002)			
	β±SE	**p value**	**HR**
Age	0.24±0.09	0.80	1.02 (0.86-1.23)
Male	-0.87±0.73	0.23	0.42 (0.10-1.75)
BMI	-0.02±0.07	0.72	0.98 (0.85-1.12)
Diagnosis		0.03	
Stable Angina	0.00		
Unstable Angina	1.14±1.56	0.46	3.12 (0.15-65.9)
NSTEMI	3.06±1.14	0.007	21.21 (2.28-197.1)
STEMI	2.42±1.44	0.09	11.26 (0.67-189.8)
Fried Frailty baseline		0.09	
Non-Frail	0.00		
Pre-Frail	-2.3±1.07	0.03	0.10 (0.01-0.82)
Frail	-1.61±1.20	0.18	0.20 (0.02-2.11)
Edmonton Frailty baseline		0.19	
Non-Frail	0.00		
Vulnerable	-2.02±1.02	0.05	7.51 (1.03-55.03)
Mild frailty	-0.29±1.32	0.83	1.33 (0.10-17.72)
Moderate frailty	-2.64±1.32	0.05	13.98 (1.06-185.0)
Severe frailty	-1.38±1.48	0.35	3.98 (0.22-72.47)

Table 6-15: Cox Hazard regression model to observe the relation of participant's diagnosis and frailty to their survival.

The relationship between frailty and mortality was explored using survival curves of the frail and non-frail cohort in the study. The survival of frail group was much lower compared to non-frail group achieving hazard ratio of 0.42.

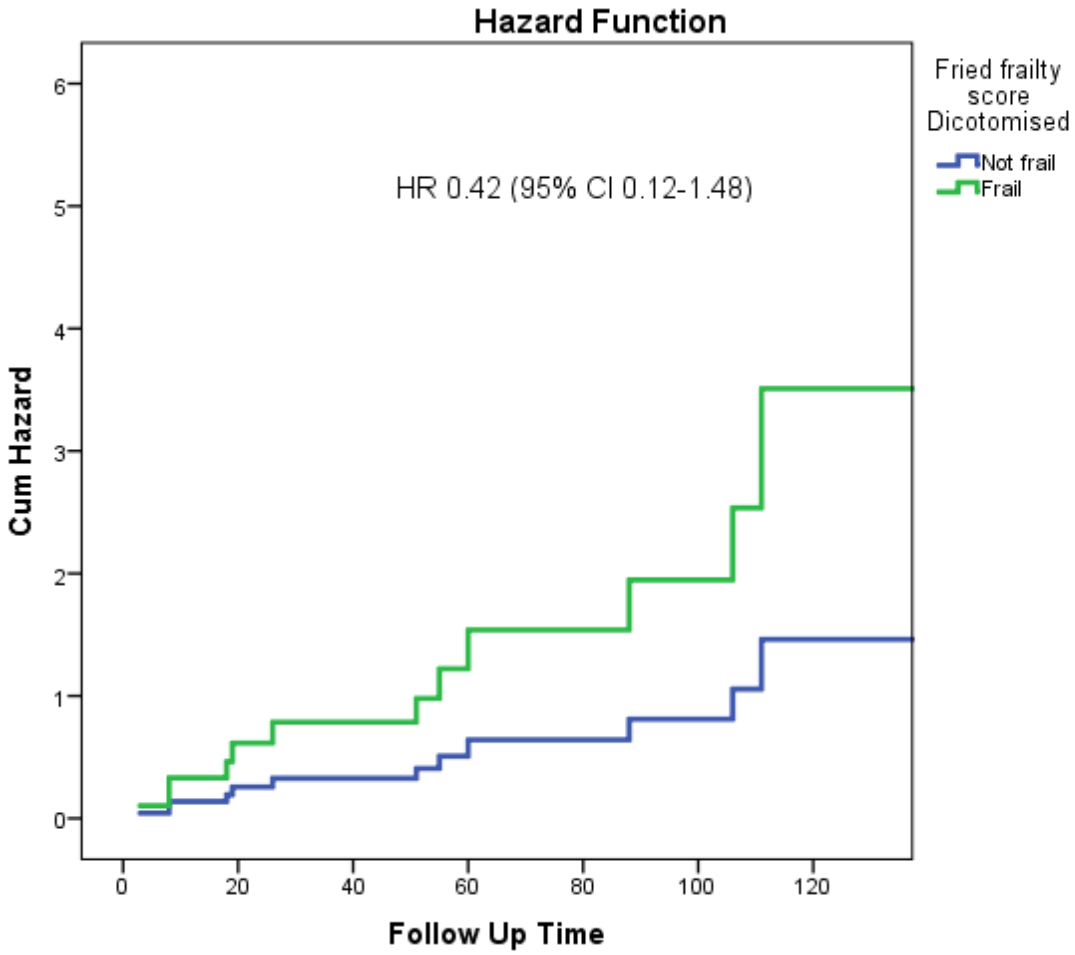


Figure 6-11: Hazard ratio for mortality as per fried frailty score dichotomised

6.3.15 ANALYSIS OF ADVERSE EVENTS IN STUDY AT FOLLOW UP

The overall mortality in the study group was 9.3% at follow up (average 107 days). This annual mortality rate is likely to be higher. The incidence of MACE which was a composite of deaths, myocardial infarction, stroke and major bleeding was around 24.7%. As the study was not powered to determine mortality significance, all the analysis was done with exploratory intentions. The distribution of adverse events across different frailty subgroups are shown in table 6-16 and 6-17.

		Fried Frailty Phenotype			
	Total Cohort (n=150)	**Not Frail (n=19)**	**Pre-frail (n=89)**	**Frail (n=42)**	**P value**
MACE	37 (24.7%)	8 (42.1%)	16 (18.0%)	13 (31.0%)	0.31
All-cause Death	14 (9.3%)	2 (10.5%)	5 (5.6%)	7 (16.7%)	0.13
MI	8 (5.3%)	2 (10.5%)	3 (3.4%)	3 (7.1%)	0.37
CVA	3 (2.0%)	1 (5.3%)	1 (1.1%)	1 (2.4%)	0.49
TIA	5 (3.3%)	1 (5.3%)	3 (3.4%)	1 (2.4%)	0.84
Major Bleed	12 (8.0%)	3 (15.85)	7 (7.9%)	2 (4.8%)	0.34
AKI	26 (17.3%)	3 (15.8%)	10 (11.2%)	13 (31.0%)	0.02

Table 6-16: Table showing complications and MACE (major adverse clinical event) as per Fried frailty phenotype

		Edmonton Frailty Score					
	Total cohort (n=150)	**Not Frail (n=78)**	**Vulnerable (n=33)**	**Mild Frailty (n=19)**	**Moderate Frailty (n=13)**	**Severe Frailty (n=7)**	**p value**
MACE	37 (24.7%)	14 (17.9%)	12 (36.4%)	5 (26.3%)	5 (38.5%)	1 (14.3%)	0.72
All-cause Death	14 (9.3%)	3 (3.8%)	6 (18.2%)	1 (5.3%)	3 (23.1%)	1 (14.3%)	0.05
MI	8 (5.3%)	3 (3.8%)	3 (9.1%)	2 (10.5%)	0 (0.0%)	0 (0.0%)	0.49
CVA	3 (2.0%)	1 (1.3%)	1 (3.0%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	0.77
TIA	5 (3.3%)	3 (3.8%)	2 (6.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.70
Major Bleed	12 (8.0%)	7 (9.0%)	2 (6.1%)	1 (5.3%)	2 (15.4%)	0 (0.0%)	0.73
AKI	26 (17.3%)	10 (12.8%)	4 (12.1%)	5 (26.3%)	5 (38.5%)	2 (28.6%)	0.11

Table 6-17: Table showing the complications and MACE (major adverse clinical event) as per Edmonton frailty score.

In essence, the incidence of frailty was markedly increase in the small number of deaths that occurred during the study course. Fifty percent of the participants that were frail.

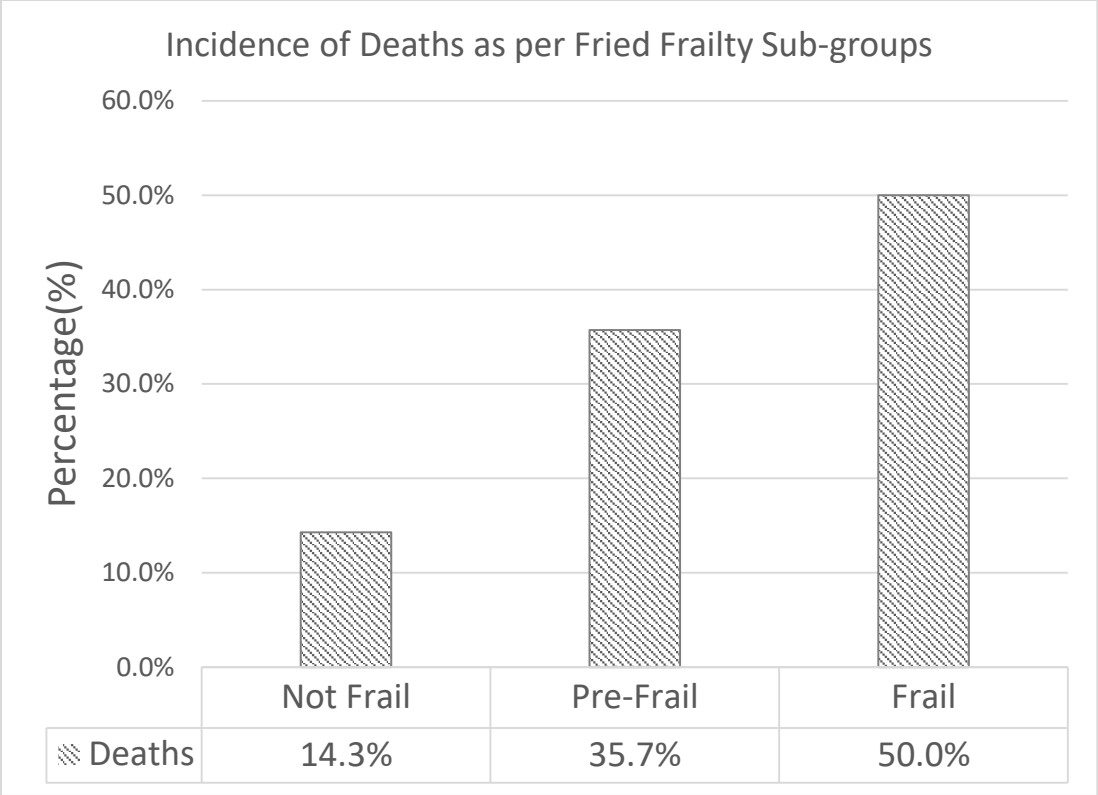


Figure 6-12: Incidence of mortality in the frailty subgroups as per Fried Frailty Phenotype.

The distribution of the adverse events in participants undergoing various management therapies is shown in table 6-18 below.

		Management Strategies			
	Total cohort (n=150)	**Medical Therapy (n=84)**	**PCI (n=51)**	**CABG (n=15)**	**p value**
MACE	37 (24.7%)	20 (23.8%)	13 (25.55)	4 (26.7%)	0.03
Death	14 (9.3%)	8 (9.5%)	6 (11.8%)	0 (0.0%)	0.39
MI	8 (5.3%)	5 (6.0%)	3 (5.9%)	0 (0.0%)	0.63
CVA	3 (2.0%)	2 (2.4%)	1 (2.0%)	0 (0.0%)	0.83
TIA	5 (3.3%)	0 (0.0%)	4 (7.85)	1 (6.7%)	0.04
Major Bleed	12 (8.0%)	5 (6.0%)	3 (5.9%)	4 (26.7%)	0.02
AKI	26 (17.3%)	11 (13.1%)	11 (21.6%)	4 (26.7%)	0.27

Table 6-18: Table showing distribution of complication as per the treatments received by the study group. MACE constituted of composite of MI, CVA and major bleeding.

6.3.16 DISCUSSION ON ADVERSE EVENTS IN THE STUDY:

There was a trend noted towards higher proportion of mortality in the frail group of participants but this did not achieve any clinical significance (FFP 16.7% vs 10.5%, p=0.13). Due to small number of events and the size of the study group generalization of any finding should be with caution. This analysis does provide us with the valuable

information to calculate sample size to power a larger scale study. Also the exact cause of death for these participants could not be determined due to access limitation. Hence, it is hard to commit that they were cardiovascular deaths.

The sub-group of patients (n=15) undergoing CABG surgery showed the least complication and no mortality. This is likely because these surgical candidates would have been pre-selected undergo surgery and anaesthetic procedures. On other hand medical and PCI group may contain patients who may have deemed unfit for surgery and offered other treatments instead. MACE and mortality seem to be evenly distributed between medical therapy and percutaneous intervention groups. A higher prevalence of stroke and TIA was observed in the group treated with percutaneous intervention. Bleeding proportions were understandably high in the surgical group. Bleeding complications in PCI group were more related to antiplatelet therapy rather than procedural bleeding complication and similar proportion to patients managed medically.

6.3.17 EFFECT OF FRAILTY STATUS ON HOSPITAL STAY

The study cohort comprised of patients admitted to hospital with acute coronary syndromes as well as out-patients treated for their stable symptoms. There were 82 (54.7%) participants who were treated as in-patients. Analysis of their frailty status and duration of stay in the hospital showed that frail participants had a much higher stay in the hospital compared to participants who were not frail. As per Friend frailty score, the mean duration of hospital stay was 6.5 days for frail patients compared to 2.7 days for patients who were not frail. The average length of stay in hospital for patients with severe frailty as determined by Edmonton frailty scale was 7.3 days (Table 6-19). This suggests that frailty adds to the economic burden of hospitalisation as frail patients take a longer time to recover. Although not explored in our study, further research should be performed to explore factors accounting for prolonged hospital stay and how this over utilization of resources can be controlled.

	Fried Frailty phenotype					
	Not Frail Mean±SD (CI)	**Pre-Frail Mean±SD (CI)**	**Frail Mean±SD (CI)**			**p value**
Length of hospital stay (days)	2.7±4.6 (0.5-4.9)	4.5±7.3 (2.9-6.0)	6.5±7.3 (4.2-8.7)			0.05
	Edmonton Frailty Score					
	Not Frail	**Vulnerable**	**Mild Frailty**	**Mod Frailty**	**Severe Frailty**	
Length of hospital stay (days)	3.4±6.7 (1.9-4.9)	6.2±7.2 (3.7-8.8)	6.1±6.2 (3.1-9.1)	6.4±8.3 (1.4-11.4)	7.3±9.4 (1.4-16.0)	0.16

Table 6-19: Table showing length of hospital stay as per frailty status of the patients.

6.4 OVERALL DISCUSSION:

The various analyses carried out on the study cohort on follow up showed that

1) The mortality rate in our study was 9.3% at mean follow up period of 114 days. The loss at follow up was also high at 22% in this study cohort of older octogenarian with symptomatic CAD.
2) The participants that died during follow up had higher mean age (85.7 vs 83.6yrs) and higher Charlson comorbidity index (8.1 vs 6.3) compared to alive participants.
3) All the management strategies including medical therapy, percutaneous intervention and CABG surgery significantly improved participants' symptoms but did not make any significant difference to their frailty and QoL although a trend towards improvement was noted.
4) The physical parameters of QoL at follow up were significantly related to baseline frailty defined by Fried frailty phenotype and NYHA Class.
5) The mental composite QoL at follow up was significantly related to baseline frailty as defined by Edmonton frailty scale.
6) Frail participants had worse survival rate compared to non-frail participants during the follow up period. Towards the end of the follow up period pre-frail and vulnerable group of patients behaved like the frail patients in the study.
7) Higher mortality numbers were noted in frail participants compared to non-frail participants in the study.

8) The frail participants in the study had longer period of stay in hospital compared to non-frail participants.

Over the last two decade there has been an increase drive for inclusion of older adult population in the trials because of the change in demographics. The older adults make up a major proportion of the patients presenting to hospital with certain health conditions like cancer and CAD. Their response and tolerability to drugs and therapies is different than the younger population. Inclusion of older participants into clinical trials cannot be over-emphasized. Review of major trials in cardiovascular disease indicated that 50% of the trials failed to enrol any participant above 75 years of age. In trials which did recruit older participants, above 75 year old constituted only 9% of all trial patients while above 85 year old represented only 2%(9). In essence we are applying guidelines on older patients based on evidence from a much young population.

However, conducting a scientific study in this age group is not without its challenges. Recruitment and retention of older adults in a trial can prove challenging(192). In our study the screening to recruitment ratio was high (181 vs 150) showing willingness of older adults to participate in a study but the loss at follow up was high (22%). The reasons deterring older participants from participating in clinical trial may vary and can be peculiar to a particular study group. This should be anticipated and catered for when designing a study in older population and measures should be taken to encourage retention. In our study, lack of means to travel to cardiac centre for follow up seemed to be the top most reason for falling out of the study. This brings to light the need for anticipating these challenges and devising a plan for them within the study design. Offering options like home visits or paid transport may significantly improve enrolment.

According to British heart foundation cardiovascular statistic report 2015, the cardiovascular mortality rate in 75-85 year old was 13.1% and 11.6% in above 85 years of age. In hospitalised older patients with acute coronary syndromes the mortality rates are expected to be much higher. The myocardial ischaemia national audit project UK report 2003-2010 suggested current in-hospital mortality rate of 19.4-20.4% in older patients above 85 years of age admitted with acute coronary syndromes. In our study the mortality rate was 9.3% at mean follow up of 114 days. With widespread availability of percutaneous intervention there has been a decline in mortality rate in patients with acute coronary syndromes over the last decade. Despite

the decline in mortality risk, older adult patients with ACS remain a high risk group who have the most to gain from percutaneous intervention. Our study observed significant improvement in the symptoms in all the treatment groups with an improvement in angina and NYHA class seen on follow up. Interestingly, these management strategies did not make any difference to the physical components of QoL but improvement in mental composite score of QoL was observed which may have been due to significant improvement in symptoms. This also suggests that the poor QoL in this patient group is not related to their symptomatic CAD. Any treatment will improve their symptoms but not necessarily their physical QoL.

Frailty was found to be significantly related to QoL both at baseline and at follow up visit. Kaplan Meier curves show that frail patients have poor survival comparatively. Hence any frailty interventions are likely to improve QoL in this group of older patients rather the treatment of their underlying CAD alone. The combination of both therapeutic and frailty intervention are likely to give these patients the maximum benefit. Exercise prescription has been suggested as a possible frailty intervention. It remains to be seen if tailoring cardiac rehabilitation to address these patient frailty needs is the way forward. Further research is needed to decide, whether therapeutic interventions along with frailty tailored cardiac prehabilitation will improves the QoL in this age group.

Comparing two well established frailty tools i.e. Fried frailty phenotype and Edmonton frailty scale to assess frailty in the same study group brought home the message that all frailty assessment tools are not alike. The Edmonton frailty scale was more predictive of the mental components of the QoL while Fried frailty scale was found to be more sensitive to the physical parameters of QoL. Neither of the two can be used as a gold standard frailty test. With a large number of frailty assessment tools available in the literature the scientific community is faced with the challenge of determining a gold standard frailty test. Larger scale studies are needed to identify and validate an ideal frailty assessment tool in this age group. It may be that frailty tests may have to be tailored according to specific group of patients. None the less, they will have to be validated to be used in that specific group of patients. With frailty research heading towards frailty intervention it is important that these frailty assessment measures are also able to identify domains of weakness in a specific frail population. Oversimplified frailty assessment tools may be useful for screening purposes but will not be able to identify the sub-domains of frailty that need targeting. The scoring system of Fried frailty phenotype makes it sensitive at screening for frailty while the graduated scoring

system of Edmonton frailty score makes it a more sensitive tool to detect any improvement or change in frailty. This may give Edmonton frailty scale in monitoring frailty and assess response to frailty interventions. American Health Association and European society of cardiology have already advocated use of frailty assessment to help improve clinical outcomes in older adult patients. We expect a continual rise in the use of frailty assessment tools in clinical practice as more and more cardiovascular interventions are being done in older patients. Another future avenue of research would be to incorporate frailty assessment as part of decision making tools used in cardiovascular multi-disciplinary team meetings and assess its impact on the decision making process.

Further research is needed into the prognosis of the pre-frail group of patients. These were patients who scored on some of the domains on frailty scores but their overall score remained below the cut off limit for frailty. It would be right to conclude that patients have some features of frailty. Number wise they constituted the largest group in our study. Analysis of Kaplan-Meier curve suggested that towards the end of the follow up period the pre-frail or the vulnerable group had poorer survival curves than the frail group which had reached the worst of its curve earlier during the follow up. This needs to be established further in a large scale study. This indicates that the pre-frail group is likely to behave like frail group down the timeline. Hence, they may benefit just as much from frailty interventions as the frail group.

6.5 CONCLUSION:

Therapeutic intervention for CAD in older adult group of patients will improve their symptoms but may not improve their physical QoL. On the other hand frailty is significantly related to QoL in this group and hence any effective frailty intervention is likely to improve QoL in such patients. Frail patients are likely to have poor survival compared to non-frail participants and stay in hospital longer.

7 CHAPTER- LABORATORY BLOOD PARAMETERS IN FRAIL PATIENTS WITH CARDIOVASCULAR DISEASE- EXPLORATION INTO BIOCHEMICAL MARKERS FOR FRAILTY.

As previously described, frailty is a geriatric syndrome which predisposes older individuals to adverse outcome when faced with clinical stressors like physical illness. Besides defining frailty with clinical and functional parameters, there has been extensive research into the biochemical processes that lead to development to frailty. Expression and downregulation of several proteins have been linked to frailty and various pathophysiological models have been proposed(193). However, due to multi-dimensional nature of frailty, a combination of biomarkers may be needed as no single biomarker has been able to predict or detect frailty (194).

In our study, we used the Fried frailty index and Edmonton frailty score to assess frailty status. These evaluate physical +/- mental abilities. However, there have been models that have suggested that routine laboratory tests have an additive value to frailty indices to identify older adult people at risk(195). In particular, there is mounting evidence of an association between vitamin D deficiency and frailty and some researchers have suggested vitamin D replacement as a plausible frailty intervention(100). The exact pathophysiological process is not clear but vitamin D deficiency downregulates inflammatory markers like IL-2 and IL-12 and increase expression of other pro-inflammatory cytokines. In addition, Vitamin D3 has been shown to have an immune modulation effects besides regulating calcium metabolism(100).

7.1 METHODS:

7.1.1 AIMS:

The main objectives of this sub-analysis were

- To identify any association between routine laboratory blood parameters with frailty. Routine blood test are readily available in clinical practice and used to screen and monitor a number of conditions. Any association of these parameters with frailty, would be easy to adopt in clinical practice.

- To explore relationship between frailty and vitamin D deficiency in older adult patients with CAD.

7.1.2 STUDY POPULATION:

The study cohort has been described in detail in chapter 4-6 and comprised of older participants (age≥80 years) with CAD, both those admitted to hospital with acute coronary syndromes and those presenting with stable angina. Patients with advanced dementia and heart failure were excluded from the study.

7.1.3 STUDY DESIGN:

Following enrolment, information about baseline blood parameters were collected (defined as full blood count and full biochemical profile taken either at recruitment or within the preceding 4-6 weeks). Levels of Vitamin D and high sensitivity C reactive protein were measured at follow up in order to avoid any effect of acute illness on these blood parameters.

7.1.4 STATISTICAL ANALYSIS

The statistical analysis was carried out on SPSS version 23 statistical analysis software. The outcome variable frailty was analysed as continuous variable. For this analysis additive scores were used for Fried frailty phenotype and Edmonton frailty scale. Initially all the blood tests were included in the predictive model to identify their association with frailty. Linear regression was used to determine the strength of this association. To determine whether these parameters could independently predict the outcome variable, they were fitted individually into the statistic model. The model was controlled for age, sex, BMI and comorbidity. Assumptions of normal distribution and equal variance were checked for each analysis. The significance level for the analysis was set at 95% (p=0.05).

7.2 RESULTS:

7.2.1 ANALYSIS OF ROUTINE LABORATORY BLOOD PARAMETERS IN FRAILTY SUB-GROUPS.

The routine blood parameters analysed are listed in the table 7-1 with their normal reference ranges. These baseline bloods also provided information about conditions like symptomatic anaemia and chronic kidney disease which may contribute to patients' symptoms in addition to the CAD alone. As the study cohort consisted of both clinically stable patients with angina, as well as patients presenting with ACS, the C - reactive protein and vitamin D levels were measured at follow up

Normal range values	
Serum Haemoglobin	
Male	135-175 g/l
Female	120-160 g/l
Moderate anaemia	70-100 g/l
Severe anaemia	<70 g/l
Neutrophil count	2.0-7.7 X 109/l
Lymphocyte count	0.8-3.4 X 109/l
Hs C-reactive protein	0-8 ng/l
Creatinine Clearance	> 60 ml/min/1.73m2
Serum Albumin	36-48 g/l
Vitamin D levels	
Adequate level	>50 ng/l
Mild Vita D deficiency	25-50 ng/l
Overt Vita D deficiency	<25 ng/l

Table 7-1: Table showing normal ranges of the laboratory blood measurements used in the analysis

To explore the relationship between these everyday laboratory blood parameters and frailty, the bloods results for the study participants were stratified according to their frailty status (Table 7-2).

Linear and backward regression was carried out to determine relationship of these blood parameters and frailty using Fried frailty phenotype and Edmonton frailty scale as outcome variable. The result of the regression model are in (table 7-3 and table 7-4). The regression analyses were controlled for age, gender, BMI and Charlson's comorbidity score. Serum haemoglobin, creatinine clearance and vitamin D level are indicative of a comorbid conditions and hence the analysis was controlled for Charlson's comorbidity score to balance out effect of concomitant comorbidity. The assumptions of linearity and equal variance were met for the regression analysis.

	Fried Score baseline				
	Total (n=150)	**Not Frail (n=19)**	**Pre-Frail (n=89)**	**Frail (n=42)**	**p value**
	Mean±SD (CI)	**Mean±SD (CI)**	**Mean±SD (CI)**	**Mean±SD (CI)**	
Serum Haemoglobin Level (g/l)	126±18 (123-129)	126±18 (117-135)	128±19 (124-132)	122±15 (118-127)	0.32
Blood neutrophil count ($x10^9$/l)	9.55±33.8 (4.06-15.04)	5.27±1.95 (4.3-6.2)	9.42±3.88 (1.72-17.12)	11.75±11.75 (0.33-23.17)	0.79
Blood lymphocyte count ($x10^9$/l)	1.85±1.83 (1.55-2.14)	1.53±0.89 (1.1-2.0)	2.0±2.21 (1.53-2.47)	1.66±1.16 (1.30-2.02)	0.45
Serum albumin level (g/l)	34±6 (34-35)	36±4 (34-38)	35±6 (33-36)	33±4 (32-35)	0.16
Creatinine Clearance (ml/min/1.73m^2)	52.6±19.9 (49.4-55.8)	55.30±14.13 (48.5-62.1)	54.32±19.37 (50.24-58.40)	47.83±22.74 (40.74-54.92)	0.18
Hs C-reactive protein level (ng/l)	n=99 13±29 (7-19)	n=13 14±30 (-4-32)	n=54 7±20 (2-13)	n=32 23±38 (9-36)	0.05
Serum Vitamin D level (ng/l)	n=86 41.6±25.8 (36.1-47.2)	n=11 51.6±18.0 (39.5-63.6)	n=50 41.3±27.4 (33.5-49.1)	n=25 37.9±25.1 (27.5-48.3)	0.34

Table 7-2: table showing various laboratory blood measurements in the frailty sub-groups as defined by fried frailty score.

	Multiple Linear regression (Adj R^2=0.196)		Backward Stepwise Regression (Adj R^2=0.225)	
	β±SE	p value	β±SE	p value
Age	0.06±0.04	0.16		
Female	0.88±0.29	0.003	0.76±0.27	0.006
BMI	-0.01±0.04	0.77		
Charlson's comorbidity score	0.17±0.06	0.008	0.16±0.06	0.007
Serum Haemoglobin Level	0.01±0.007	0.10	0.02±0.007	0.02
Blood neutrophil count	0.003±0.005	0.55		
Blood lymphocyte count	-0.009±0.06	0.89		
Serum albumin level	-0.09±0.03	0.01	-0.08±0.03	0.009
Hs C-reactive protein	-0.002±0.005	0.62		
Creatinine Clearance	0.01±0.008	0.29		
Serum Vitamin D Level	-0.01±0.005	0.05	-0.01±0.005	0.03

Table 7-3: Multiple variable linear regression and stepwise backward regression showing relationship between various laboratory measurements and frailty as defined by fried frailty phenotype.

Edmonton Frailty cumulative score Baseline	Multiple Linear regression (Adj R^2=0.348)		Backward Stepwise Regression (Adj R^2=0.343)	
	β±SE	p value	β±SE	p value
Age	0.02±0.09	0.83		
Female	2.80±0.62	0.00	2.43±0.57	0.000
BMI	-0.12±0.07	0.13		
Charlson's comorbidity score	0.56±0.13	0.00	0.49±0.12	0.000
Serum Hemoglobin Level	0.03±0.02	0.07	0.03±0.01	0.02
Blood neutrophil count	0.02±0.01	0.05		
Blood lymphocyte count	-0.09±0.13	0.51		
Serum albumin level	-0.21±0.07	0.004	-0.20±0.06	0.003
C-reactive protein	-0.01±0.01	0.30		
Creatinine Clearance	0.03±0.02	0.14		
Serum Vitamin D Level	-0.02±0.01	0.04	-0.02±0.01	0.03

Table 7-4 : Multivariable regression analysis and backward stepwise analysis showing relationship of various blood results parameters and their association with cumulative Edmonton frailty score.

7.2.2 *DISCUSSION ON LABORATORY BLOOD PARAMETERS ANALYSIS*

Our results do not demonstrate that frail patients are significantly more anaemic than their non-frail counterparts. We did however find that the neutrophil levels were increased in the frail cohort. Whilst this might be explained by the diagnosis of ACS in many of these patients, frailty has in itself been linked to chronic immune activation. In study of 1106 older women, there was a significant and positive correlation between the frailty score and neutrophil count, but a significantly negative correlation to the lymphocyte count(94). In addition we also found that at follow-up, frail patients with CAD had a higher HS-CRP level. Review of studies of inflammatory markers in frail patients, suggest an association between raised CRP and frailty in older adults(196). However this association does not seem to be highly specific.

There is an association between nutritional status and frailty. As a marker of nutritional status we evaluated levels of albumin and found that there was numerically lower levels of albumin in the frail cohort though this did not reach statistical significance (p=0.16). Hong et al studied the relationship between nutrition related biomarkers and frailty in 380 older hospitalized patients and concluded that patients with better nutritional status and higher levels of total protein and albumin were less likely to develop frailty (197, 198).

The average vitamin D level of the cohort was mildly reduced at 41.6±25.8 ng/l (23.1-47.2). It is important to note that recruitment was done mainly in the autumn and winter with lower sunlight exposure. Such seasonal variation in vitamin D level are well documented. In a Swedish cohort study, during January till March vitamin D levels below the thresholds of 50 and 75 nmol/L were observed in 58 and 88 % of the participants(199). In our study the frail participants' vitamin D levels were towards the lower end of the spectrum compared to the non-frail group (37.9 vs 51.6 ng/l, p=0.34). Likewise the frail participants had lower creatinine clearance compared to non-frail group (47.8 vs 49.4 ml/min/1.73m2, p=0.18).

Regression analysis was performed to further assess relation of frailty with these laboratory markers. Charlsons' comorbidity score, serum haemoglobin level, serum albumin level and serum Vitamin D levels were significantly related to the Fried frailty score. This model had adjusted R square value of 0.225 suggesting that the model could explain 22.5 % of the variability in data. Same predictor variables attained significance when the analysis was repeated using cumulative Edmonton frailty scores as the outcome variable. The adjusted R square value for this analysis was 0.343.

7.2.3 Relationship between Vitamin D deficiency and Frailty:

Initial analysis of the blood parameters suggested that vitamin D levels were a strong predictor of frailty. Vitamin D deficiency has been linked to frailty and could be a modifiable frailty intervention. To explore this relationship further, study cohort's clinical characteristics were grouped according to their vitamin D levels. Vitamin D levels of less than 25nmols/l were taken as overt Vitamin D deficiency. Levels between 25 and 50nmols/l were taken as mild vitamin D deficiency while levels above 50nmols/l were considered to indicate adequate vitamin D reserves. Vitamin D levels of 87 participants were available, who were included in the analysis. Participants already on Vitamin D were excluded. Initial comparison of the variables suggested a significant difference in vitamin D levels for gender, Fried frailty phenotype and SF-12 physical composite scores (Table 7-5).

		Overt Vitamin D Deficiency (n=29) (< 25 nmols/l)	Mild Vitamin D Deficiency (n=28) (25-50 nmols/l)	Adequate Vitamin D Levels (n=30) (>50 nmols/l)	p value
Age		83.9±3.1 (82.7-85.1)	84.0±3.6 (82.6-85.4)	83.2±2.7 (82.2-84.3)	0.54
Male		16 (55.2%)	24 (85.7%)	22 (73.3%)	0.04
Female		13 (44.8%)	4 (14.3%)	8 (26.7%)	0.04
BMI		27.6±4.2 (26.0-29.2)	28.5±5.1 (26.5-30.4)	26.8±3.2 (25.6-28.0)	0.47
Charlson's Comorbidity score		6.7±2.1 (5.9-7.5)	7.0±2.6 (6.0-8.0)	6.4±1.6 (5.8-7.0)	0.48
Fried Score baseline	**Not Frail**	2 (6.9%)	1 (3.6%)	8 (26.7%)	0.04
	Pre-Frail	16 (55.2%)	21 (75.0%)	14 (46.7%)	
	Frail	11 (37.9%)	6 (21.4%)	8 (26.7%)	
Edmonton Score baseline	**Not Frail**	11 (37.9%)	17 (60.7%)	20 (66.7%)	0.21
	Vulnerable	5 (17.2%)	7 (25.0%)	5 (16.7%)	
	Mild Frailty	8 (27.6%)	2 (7.1%)	4 (13.3%)	
	Moderate Frailty	4 (13.8%)	1 (3.6%)	1 (3.3%)	
	Severe Frailty	1 (3.4%)	1 (3.6%)	0 (0.0%)	
SF-12 PCS score baseline		33.7±11.2 (29.4-38.0)	37.4±8.3 (34.2-40.6)	39.6±11.2 (35.4-43.8)	0.09
SF-12 MCS score baseline		52.9±10.7 (48.9-57.0)	48.2±13.2 (43.1-53.3)	54.1±11.3 (49.9-58.3)	0.19

Table 7-5: Table showing characteristics of study cohort as per their vitamin D levels

To determine whether vitamin D levels could be independent predictor of frailty, further linear regression was carried out with vitamin D levels as predictor variable controlling for age, sex and Charlson's comorbidity score. The analysis suggests a strong relationship between overt vitamin D deficiency and Fried frailty phenotype (p=0.02) and Edmonton frailty score (p=0.01). This model had adjusted R square values of 0.422 and 0.226 respectively. The results were reproducible when analysis was repeated using cumulative Edmonton frailty score as the outcome variable. Assumptions for the analysis were met. The details of the analysis are given in Table 7-7 and Table 7-8.

Fried Frailty cumulative score at follow up	**Multiple Linear regression (Adj R^2=0.413)**		**Backward Stepwise Regression (Adj R^2=0.422)**	
	β±SE	**p value**	**β±SE**	**p value**
Age	0.11±0.04	0.004	0.12±0.04	0.001
Female	0.76±0.25	0.004	0.76±0.25	0.003
BMI	-0.02±0.03	0.45		
Charlson's comorbidity score	0.30±0.05	0.00	0.30±0.05	0.00
Vitamin D Level				
Overt deficiency (<25)	0.69±0.28	0.02	0.58±0.24	0.02
Mild deficiency (25-50)	0.20±0.29	0.49		
Adequate levels (>50)	0.00			

Table 7-6: Linear Regression showing relationship between frailty and vitamin d deficiency.

Edmonton Frailty cumulative score at follow up	**Multiple Linear regression (Adj R^2=0.223)**		**Backward Stepwise Regression (Adj R^2=0.226)**	
	β±SE	**p value**	**β±SE**	**p value**
Age	0.06±0.09	0.64		
Female	0.83±0.62	0.18		
BMI	-0.12±0.07	0.09	-0.15±0.07	0.03
Charlson's comorbidity score	0.56±0.13	0.00	0.56±0.13	0.00
Vitamin D Level				
Overt deficiency (<25)	0.99±0.67	0.15	1.46±0.56	0.01
Mild deficiency (25-50)	-0.51±0.70	0.47		
Adequate levels (>50)	0.00			

Table 7-7: Linear regression showing relationship between frailty and vitamin d deficiency using Edmonton frailty score.

7.2.4 *RELATIONSHIP BETWEEN MILD TO MODERATE ANAEMIA AND FRAILTY:*

During the initial regression model serum haemoglobin and albumin level also gained significance as predictor variables for frailty. Regression analysis was repeated separate for anaemia and albumin levels to determine whether they could independently predict frailty. It must be noted that the participants in the cohort had mild to moderate anaemia only. There was only one participant whose Hb level was below 70g/l. Contrary to the initial analysis anaemia did not gain statistical significance (p=0.60.0.30) as an independent predictor for fried frailty phenotype (Table 7-9)

Fried Frailty cumulative score baseline	**Multiple Linear regression (Adj R^2=0.176)**		**Backward Stepwise Regression (Adj R^2=0.168)**	
	β±SE	**p value**	**β±SE**	**p value**
Age	0.08±0.03	0.01	0.70±0.03	0.02
Female	0.61±0.21	0.004	0.55±0.20	0.007
BMI	0.04±0.02	0.12		
Charlson's comorbidity score	0.18±0.04	0.00	0.19±0.04	0.00
Anaemia				
No anaemia	0.00			
Mild anaemia(M 100-135,F100-120)	0.22±0.21	0.30		
Moderate anaemia (70-100g/l)	-0.19±0.36	0.60		

Table 7-8: Multiple variable linear regression to determine relationship of anaemia to frailty at baseline. Moderate anaemia was defined as Hb less than 10 while mild anaemia was defined as Hb above 10 till the gender specific normal Hb range (M 135-175,F 120-160)

7.2.5 *RELATIONSHIP BETWEEN SERUM ALBUMIN AND FRAILTY:*

Similarly regression analysis was carried out using serum albumin as an independent predictor for Fried frailty phenotype. Although the analysis, did not gain statistical significant association, but it came very close to the set level of significance (p =0.07). See table 7-9. It may be that, on a larger size cohort this association may prove to be significant. Serum albumin has been used in some of the older frailty assessment tools as a marker of poor nutritional state however these frailty tools have not been extensively used or validated. Questionnaire based frailty assessment tools are more practical as they can be completed via post as well.

Fried Frailty cumulative score baseline	Multiple Linear regression (Adj R^2=0.191)		Backward Stepwise Regression (Adj R^2=0.182)	
	β±SE	p value	β±SE	p value
Age	0.08±0.03	0.01	0.06±0.03	0.03
Female	0.60±0.20	0.003	0.58±0.20	0.04
BMI	0.03±0.02	0.10		
Charlson's comorbidity score	0.18±0.04	0.00	0.19±0.04	0.00
Serum Albumin Level	-0.03±0.02	0.06	-0.03±0.02	0.07

Table 7-9: Linear regression showing relationship between serum albumin and frailty as per fried frailty phenotype

7.3 OVERALL DISCUSSION:

This analysis exploring association between everyday blood laboratory parameters and frailty have highlighted few important points.

- There seems to be a significant inverse association between serum albumin, severe vitamin D deficiency and frailty. Both of these factors showed evidence of being independent predictors of frailty when controlled for age, sex and comorbid conditions.

- Mild to moderate anaemia initially showed evidence of being a significant predictor in mixed model regression but does not seem to be an independent predictor of frailty. There were no patient with severe anaemia in the study cohort.

Serum albumin is mainly synthesized in liver and in specific clinical situation like chronic liver disease can be used as a marker for the organ's synthetic function. However the level of albumin protein in blood is dependent on intricate interaction of multiple physiological and pathophysiological process and hence not always specific of liver function. Interestingly low serum albumin has been associated with limitation of activities of daily living and a risk of future decline in functional performance (200). This association has been shown both in cross-sectional and longitudinal studies. Jensen et al demonstrated that albumin level of less than 35g/l was associated with functional limitation while Schalk et al in their longitudinal study suggested that that low serum albumin poses increase risk of future decline in functional state (200, 201). Our study demonstrated association between low serum albumin and higher frailty scores. This relationship was reproducible both with Fried Frailty Phenotype and Edmonton frailty score giving it more substance. We would interpret this finding as an association as study was observational in nature without any matched control groups. Larger size randomised control trial would be required to further explore this

association further. Because of multiple physiological controls influencing the serum albumin levels, it cannot be used as screening test for frailty but it may have a role in risk stratifying older patients with frailty. More evidence is needed in this regard. Similarly this association does not suggest any causality but a possible association.

Association of vitamin D deficiency with frailty in older adult population has been suggested by a number of studies, systemic reviews and meta-analysis(202-206). Our study found a similar relationship between vitamin D deficiency and frailty in patients with symptomatic coronary artery disease, attaining significance at very low vitamin D levels. Again this association does not suggest any causality. A reverse causal relationship can also exist as frailty restricts physical function and in theory can decrease exposure to sunlight leading to low vitamin D levels. Vitamin D deficiency is an easy modifiable predictor of frailty and perhaps can be used as a possible frailty intervention. Evidence in this area is lacking and further research in needed. Our study results also showed that participants with overt vitamin D deficiency had lower physical QoL. Their SF-12 physical composite score were significantly lower compared to participants with adequate vitamin D levels. Such a difference was not detected in mental quality of life parameter scores. This can suggests that the effect of vitamin D deficiency is due to restriction of physical performance.

Biochemical parameters remains a rich area for future frailty research. Due to multi-dimensional nature of frailty syndrome, no single measurable biochemical blood parameter will be sensitive enough to detect or predict frailty. But adding serum albumin levels or vitamin D level may improve the predictive value of present frailty assessment tools. Further research is needed in this area.

7.4 CONCLUSION:

Overt Vitamin D deficiency and hypoalbuminemia are independent predictors of frailty in older adult patients with symptomatic coronary disease. There is no single laboratory biomarker of frailty in this study cohort of older adult participants.

8 CHAPTER- RESEARCH CONCLUSIONS AND RECOMMENDATIONS FOR FURTHUR RESEARCH

A number of analyses were performed on the available data to determine the variables that were likely to significantly impact the outcome that is QoL of older patients presenting with symptomatic CAD. Within the limitations of the study, it has outlined a clear picture. It not only adds to the current evidence base but also bridges some of the knowledge gap. In this concluding chapter, the special features of the study have been summarised and areas of further research have been outlined.

8.1.1 HOLISTIC REAL LIFE OBSERVATIONAL STUDY WITH FOCUS ON MEDICALLY MANAGED PATIENTS.

This study gives a very holistic real life observational picture focussing on a select age group of older adult patients with coronary artery disease. There is scarcity of robust evidence in this age group who formed either a minor group or were excluded from large landmark cardiovascular studies. This study included nonselective consecutive patients across the whole spectrum of acute coronary syndrome including patients with stable angina and also who were managed with medical therapy. This is still an uncommon scenario in present day literature. Medically managed patient group is usually not focussed on in most of the coronary interventional studies, yet in this age group of older octogenarian, medical therapy is usually the main line of management.

8.1.2 DIFFICULTIES IN CARRYING OUT CLINICAL STUDIES IN OCTOGENARIAN POPULATION.

Carrying out a research study in older age group is not easy. Our study was no exception. Any researcher planning a study in older age group should anticipate slow recruitment and high rate of loss at follow up. In our study this was around 24% excluding the deaths in the study. The main issues identified were slow recruitment and difficulty in transport to come for follow up appointments. These factors should be accounted for when designing a study for this age group.

8.1.3 PREVALENCE OF FRAILTY IN OLDER ADULT PATIENTS WITH CORONARY ARTERY DISEASE IN HOSPITAL SETTING.

The prevalence of Frailty in the study cohort was 28% by Fried Frailty score and 26.1% by Edmonton Frailty scale. This study was in a hospital based setting. The mortality rate was 9.3% at 114 days. These values can be used to calculate cohort

size required for larger size studies on frailty in similar age group and characteristics in hospital setting.

8.1.4 EVIDENCE ON CONSIDERABLE OVERLAP BETWEEN FRAILTY, CO-MORBIDITY AND DISABILITY IN OLDER ADULT PATIENTS

We objectively measured the degree of overlap between frailty comorbidity and disability in the study cohort. We found out that 73.8% of the participants were frail with at least one major comorbidity and disability on the IADL scores. This is particularly important for future research, as any frailty intervention in this age group will also need to address comorbidities and disability to attain desired frailty outcomes.

8.1.5 EVIDENCE ON UTILITY OF FRIED FRAILTY SCALE AND EDMONTON FRAILTY SCALE IN OLDER ADULT PATIENTS

There are numerous frailty assessment tools outlined in the literature. We used two frailty assessment tools namely Fried Frailty score and Edmonton frailty scale to assess frailty in our study cohort. There are only a few studies demonstrating their utility in octogenarian cohort. We found concordance between their findings giving internal validity to the study. There is no gold standard frailty assessment tools as yet. We measured scores that offered the best sensitivity and specificity to detect significant frailty that would affect QoL in older patients. A cut off score of 1.50 of Fried frailty scale was found to have sensitivity of 70% and a specificity of 86% to detect significant physical frailty in the prescribed study cohort. While a cut-off score of 3.50 and 4.50 on Edmonton frailty score offered a good balance of sensitivity and specificity to detect physical frailty. This is new evidence which needs to be validated with larger scale studies. Our study also evidences the feasibility of use of these frailty scores as screening tools in octogenarians with CAD.

8.1.6 EVIDENCE ON EFFECT OF FRAILTY SCORES CONSTRUCT ON THEIR SENSITIVITY

We demonstrated that all frailty scores are not the same. The way they are constructed has impact on their sensitivity and specificity. An unexpected observation in our study was that Fried frailty score was better at predicting physical parameters of quality of life while Edmonton Frailty scale was showed better association with mental parameters of health related quality of life.

8.1.7 EVIDENCE ON EFFECTIVE USE OF SF-12 IN OLDER ADULT POPULATION

Similarly there is very limited evidence citing use of SF-12 quality of life questionnaire in octogenarian population. In our study experience the participants were able to understand and complete the questionnaire without being burdened by the question load.

8.1.8 EVIDENCE ON NEGATIVE CORRELATION BETWEEN FRAILTY AND QUALITY OF LIFE IN OCTOGENARIANS WITH CORONARY ARTERY DISEASE

Our study found a significant negative correlation between frailty and quality of life in older adult participants with coronary artery disease. Frail participants had higher symptom burden. This high symptom load was also associated with poor physical QoL. For mental quality of life parameters this association was less robust. However, Frailty continues to show significant negative correlation with quality of life in addition to the symptom load in the final regression model.

8.1.9 EVIDENCE ON LACK OF SIGNIFICANT IMPROVEMENT INPHYSICAL QUALITY OF LIFE WITH VARIOUS MANAGEMENT STRATEGIES FOR CORONARY ARTERY DISEASE IN OCTOGENARIAN PATIENTS

When participants were assessed at their follow up after receiving treatments for their underlying CAD, it was observed that the treatments they had received did not significantly improve their frailty status but did improve their symptoms. Similarly, treatments including medical therapy, percutaneous intervention and surgery did not make any difference to the physical parameters of QoL but did significantly improve the mental parameters of QoL. This is an important finding as it suggests that only treating the underlying CAD may improve the symptoms of the older adult patients but might not make any difference to their frailty and physical QoL. This need to be confirmed by a large scale study as a trend towards improvement was seen but did not achieve statistical significance.

8.1.10 EVIDENCE ON RELATIONSHIP BETWEEN POOR SURVIVAL AND FRAILTY IN OLDER ADULT PATIENTS WITH CORONARY ARTERY DISEASE.

Due to small cohort size it was impossible to determine significant predictors for death in the study. However Kaplan-Meire survival curve indicated that frail participants had poor survival. Another important trend that was observed was

that the pre-frail/vulnerable group showed a drop in survival towards the end of observed period almost behaving like the frail cohort. Further research is needed to characterise the pre-frail group and determine whether they are likely to benefit more from frailty intervention than established frail patient.

8.1.11 EVIDENCE ON PROLONGED HOSPITAL STAY IN FRAILTY PATIENTS SUGGESTING COSTLY ECONOMIC BURDEN

Frail patients pose a higher economic burden for healthcare. In our study carried out in a hospitalised setting frail participants stayed twice as long as inpatient compared to non-frail participants.

8.1.12 EVIDENCE ON ASSOCIATION OF SEVERE VITAMIN D DEFICIENCY AND FRAILTY

As described in chapter 7, severe vitamin D deficiency (<25 ng/dl) showed association with frailty however a large scale study is needed to explore this further.

8.2 LIMITATIONS OF STUDY:

8.2.1 LIMITATIONS OF STUDY DESIGN:

The FRAIL-HEART study has been designed on a cohort based observational model with non-probability prospective sampling. Observational study design comes with its own limitation. Still, this model would be appropriate for an exploratory study into this select population of older people in their last decade of life. To conduct a randomised control trial (RCT), the gold standard research design, in this population would be difficult due to small sample size and limited survival rates. Research studies in older population have traditionally found it hard to recruit participants. The challenges include increased prevalence of cognitive impairment in this age group precluding informed consent, travel to the research facilities and high drop off rate during follow-ups(207). An observational design of the study allowed participants to be monitored as part of their healthcare journey within its limitations.

The potential of bias are higher in observational study and cannot be always eliminated. In FRAIL-HEART study there can be selection bias as the cohort is based on patients presenting to the hospital. This is essence makes the study cohort a selected group. Hence the findings of the study should be applied to in-patients and cannot be generalised to the community population. This limits the scope of the study.

FRAIL-HEART is a single centre based study. Being carried out in a single tertiary care centre will reduce its external validity and the results will be prone to bias resulting from practices peculiar to a particular hospital or geographic area.

People with significant cognitive impairment were excluded from the study due to inability to consent. Also cognitive impairment negatively effects the mental parameters of quality of life. Excluding patients with cognitive impairment from the study can introduce bias.

8.2.2 LOSS TO FOLLOW-UP:

Cohort based prospective observational studies have the advantage of identifying an association between an exposure and outcome and can also yield incidence rate and relative risks, but usually the interval between the exposure and development of outcome is kept short to minimize loss to follow-up(208). The limited survival rates of the older adult in study group will add to this equation. To reduce loss to follow-up, early follow up at 4 months was planned. Frail patients tend to have high mortality and morbidity prevalence which can introduce a differential loss to follow-up in this high risk group.

8.2.3 SMALL SAMPLE SIZE:

The prospective cohort design of the FRAIL-HEART study will allow a diverse group, including angina, NSTEMI and STEMI, to be observed but the small sample size will limit the study to power any outcome. This will be an exploratory study and will pave way for a larger cohort study. Presence of association does not always indicate causation. In observational studies, Hill criteria is usually applied to determine a causal relationship(209). The larger the magnitude of the observed association the more likely is that a casual process exists. Small sample size will make it harder to assess the magnitude of the observed correlation. A larger study will be needed to validate its findings.

8.2.4 PRECISION AND VALIDITY:

In observational studies random variation can occur because of the sampling technique used and the way in which different variables are measured. This can compromise the precision of the study which reflects lack of random error. As the sample size of the FRAIL-HEART study is comparatively small it will be prone to random error. It will hence be preferable to get balanced group of frail and non-frail participants in the study. The non-frail group in the study cohort will behave as a control group to establish internal validity of the study and rule out any systemic

error. However the study will lack external validity due to the hospital based setting of the study and being a single centre study. The study results will not apply to population in general.

8.2.5 ASSESSMENT OF ST ELEVATION MYOCARDIAL INFARCTION PATIENTS:

In prospective observational studies the exposure is ascertained before the outcome. In case of patient presenting with an ST elevation myocardial infarction, this was not be possible in present study design. However they were included in the study as a high risk group and assessed once they are stable enough to undergo study assessments. These assessments may not reflect their precise pre-morbid condition but will be allowed as baseline for this particular subgroup. Unlike other groups in the study the STEMI patients were recruited after they had their treatment. They were assessed once they had been cleared by the cardiac physiotherapist.

8.3 RECOMMENDATIONS FOR FURTHER RESEARCH:

1) Further large scale trials are needed to compare medical therapy with percutaneous coronary intervention strategy in older adult age group.
2) There is a significant overlap between frailty, comorbidity and disability in older age group like the study group. Further research is needed regards how this overlap will affect the outcome of any frailty intervention in this age group.
3) There is no gold standard frailty tool and it may not be possible to have one either. There is an ever increasing number of frailty tools in scientific literature. Extensive research is required to validate most of them and if possible to formulate a single assessment tool if at all possible.
4) Kaplan-Meier survival curve put a spot light on the pre-frail group which started behaving like the frail group towards the end of the observed period. Further research should focus not only the frail group but also on the pre-frail group to identify patients that are likely to progress to full blown frailty. Furthermore impact of frailty intervention on this pre-frail group would be a rich ground for further research.
5) The relationship of severe vitamin D deficiency on frailty in this age group needs to be further explored with a larger scale study to cater for seasonal variation. Further research is also needed as role of vitamin D replacement as a possible frailty intervention.
6) Our study showed a strong correlation between frailty and health related QoL. Exercise prescription has been used as frailty intervention. A rich area of

research would be to investigate the effects a frailty tailored cardiac prehabilitation programme on the QoL of this older adult population with CAD

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10 APPENDICES

10.1 APPENDIX-1-SF-12 HEALTH SURVEY QUESTIONNAIRE(162)

This survey asks for your views about your health. This information will help you keep track of how you feel and how well you are able to do your usual activities.

Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

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1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
○	○	○	○	○

---

2. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
A <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○	○	○
B Climbing <u>several</u> flights of stairs	○	○	○

---

3. During the <u>past 4 weeks</u>, have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	Yes	No
A <u>Accomplished less</u> than you would like	○	○
B Were limited in the <u>kind</u> of work or other activities	○	○

---

4. During the <u>past 4 weeks</u>, have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	Yes	No
A <u>Accomplished less</u> than you would like	○	○

B Did work or other activities less carefully than usual	○	○

---

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
○	○	○	○	○

---

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
A Have you felt calm and peaceful?	○	○	○	○	○	○
B Did you have a lot of energy?	○	○	○	○	○	○
C Have you felt downhearted and blue?	○	○	○	○	○	○

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7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
○	○	○	○	○

10.2 APPENDIX-2- FRIED'S FRAILTY PHENOTYPE(46)

10.2.1 WEIGHT LOSS:

"In the last year, have you lost more than 10 pounds weight unintentionally (i.e., not due to dieting or exercise)?"

YES NO

"At follow up visit weigh the patient and calculate K as follow	Weight at Follow up visit:
(Weight in previous year – current measured weight)/ (weight in previous year) =K.	K value =

10.2.2 EXHAUSTION:

"How often in the last two weeks did you feel that everything you did was an effort or you could not get going?"

0=rarely or none of the time (≤1 day)	1=some or a little of the time (1-2 days)	2= a moderate amount of time (3-4 days)	3=most of the time

10.2.3 PHYSICAL ACTIVITY: (MINNESOTA LEISURE TIME ACTIVITY QUESTIONNAIRE)

ACTIVITY (MET Value)	Did you perform this activity during the last two weeks?		How many sessions of this activity did you do during the last two weeks?	How long did you usually do the activity each time?	
	Yes	No		Hours	Mins
Walking for exercise (3.5)					
Moderate strenuous house chores (3.5)					
Lawn mowing (5.5)					
Lawn raking (4.3)					
Gardening (4.0)					
Hiking (6.0)					

Jogging (7.0)					
Biking (8.0)					
Exercise Cycle (10.5)					
Dancing (4.5)					
Aerobics (6.5)					
Bowling (3.0)					
Golf (4.5)					
Singles tennis (8.0)					
Doubles Tennis (5.0)					
Racquet ball (7.0)					
Calisthenics/Weights (3.5-8.5)					
Swimming (6.0)					

Note: Energy expenditure (kcal/week) was determined using metabolic equivalent (MET) score: **(activity specific MET)x ((activity duration in minutes)/60) x (number of sessions in past two weeks)/2)).** Energy expenditure was calculated by summing expenditures over all activities/number of activities done.

10.2.4 GAIT SPEED:

Can you please walk for 15 feet (4.6 m) at your normal walking pace?	Walking Time (secs)
Without walking aid	
With walking aid	

10.2.5 GRIP STRENGHT:

Can you please grip this as hard as you can. (The best measurement counts)		
1st Reading:	2nd Reading:	3rd Reading:

10.2.6 CRITERIA USED TO DEFINE FRAILTY

10.2.7 WEIGHT LOSS:

"In the last year, have you lost more than 10 pounds unintentionally (i.e., not due to dieting or exercise)?" If yes, then frail for weight loss criterion. At follow-up, weight loss was calculated as: (Weight in previous year – current measured weight)/ (weight in previous year) =K. If K ≥ 0.05 and the subject does not report that he/she was trying to lose weight (i.e., unintentional weight loss of at least 5% of previous year's body weight), then frail for weight loss = Yes.

10.2.8 EXHAUSTION:

Using the CES–D Depression Scale, the following two statements are read. (a) I felt that everything I did was an effort; (b) I could not get going. The question is asked "How often in the last week did you feel this way?" 0= rarely or none of the time (≤1 day), 1= some or a little of the time (1–2 days), 2= a moderate amount of the time (3–4 days), or 3= most of the time. Subjects answering "2" or "3" to either of these questions are categorized as frail by the exhaustion criterion.

10.2.9 PHYSICAL ACTIVITY:

Based on the short version of the Minnesota Leisure Time Activity questionnaire, asking about walking, chores (moderately strenuous), mowing the lawn, raking, gardening, hiking, jogging, biking, exercise cycling, dancing, aerobics, bowling, golf, singles tennis, doubles tennis, racquetball, calisthenics, swimming. Kcals per week expended are calculated using standardized algorithm. This variable is stratified by gender.

Men: Those with Kcals of physical activity per week ≤383 are frail.

Women: Those with Kcals per week ≤270 are frail.

10.2.10 WALK TIME:

Stratified by gender and height (gender-specific cut-off a medium height).

Men	Cut-off for Time to walk 5 metre criterion for frailty
Height ≤173 cm	≥7 seconds
Height >173 cm	≥6 seconds
Women	
Height ≤159 cm	≥7 seconds
Height >159 cm	≥6 seconds

10.2.11 GRIP STRENGTH:

Stratified by gender and body mass index (BMI) quartiles:

Men	Cut-off for grip strength (Kg) criterion for frailty
BMI ≤ 24	≤29
BMI 24.1–26	≤30
BMI 26.1–28	≤30
BMI >28	≤32
Women	
BMI ≤23	≤17
BMI 23.1–26	≤17.3
BMI 26.1–29	≤18
BMI >29	≤21

10.3 APPENDIX-3- EDMONTON FRAILTY SCORE(118)

ITEM		0 POINT	1 POINT	2 POINT
Please imagine that this pre-drawn circle is a clock. I would like you to place the numbers in the correct positions then place the hands to indicate a time of 'ten past eleven'.		No errors	Minor spacing errors	Other errors
In the past year, how many times have you been admitted to the hospital?		0	1-2	≥2
In general how would you describe your health?		Excellent/Very good/Good	Fair	Poor
With how many of the following activities do you require help? meal preparation, shopping, transportation, telephone, housekeeping, laundry, managing money, taking medication		0-1	2-4	5-8
When you need help, can you count on someone who is willing and able to meet your needs?		Always	Sometimes	Never
Do you use five or more different prescription medications on a regular basis?		No	Yes	
At times do you forget to take your medications?		No	Yes	
Have you recently lost weight such that your clothing has become looser?		No	Yes	
Do you often feel sad or depressed?		No	Yes	
Do you have a problem with losing control of urine when you don't want to?		No	Yes	
I would like you to sit in this chair with your back and arm resting. Then when I say GO please stand up and walk at a safe and comfortable pace to the mark on the floor approx. 3 m away, return to the chair and sit down.		0-10 sec	11-20 sec	>20 sec/pt unwilling /requires assistance
Final score: (sums of column total)				
Scoring: 0-5= Not Frail	0:	3:	9:	24:

6-7=Vulnerable 8-9=Mild Frailty 10-11= Moderate Frailty 12-17= Severe Frailty				

11.1 APPENDIX-4- CHARLSON COMORBIDITY INDEX SCORING SYSTEM(210).

Score	Condition
1	Myocardial infarction (history, not ECG changes only) Congestive heart failure Peripheral disease (includes aortic aneurysm >= 6 cm Cerebrovascular disease: CVA with mild or no residua or TIA Dementia Chronic pulmonary disease Connective tissue disease Peptic ulcer disease Mild liver disease (without portal hypertension, includes chronic hepatitis) Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia Moderate or severe renal disease Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes) Tumour without metastasis (exclude if > 5 y from diagnosis) Leukaemia(acute or chronic) Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumour AIDS (not just HIV positive)

NOTE: For each decade more than 40 years of age, a score of 1 is added to the above score. The Charlson comorbidity index predicts the ten-year mortality for a patient who may have a range of comorbid conditions, such as heart disease, CVA, or cancer (a total of 22 conditions). Each condition is assigned a score of 1, 2, 3, or 6, depending on the risk of dying associated with each one. Scores are summed to provide a total score to predict mortality

11.2 APPENDIX-5- A SYNOPSIS OF FRAILTY ASSESSMENT INSTRUMENTS.

More than 20 assessment tools have been proposed to assess frailty in older adult population(101). Broadly researchers have taken two directions in assessment of frailty. One set of instrument assess what the person can do either by performing physical tasks or answering relevant questions while others have assessed frailty by accumulation of deficits or things a person can't do. These frailty assessment tools have been around for more than a decade. They have been designed for specific purpose or population in mind and not always covered all the recognised domains of frailty as recognised today. Social support, cognition and mood are domains which are featured more in the frailty assessments tools developed during the latter years.

Following is a systemic review of literature and frailty assessment tools.

11.2.1 SPEECHLEY AND TINETTI ET AL(104).(1991)

STUDY POPULATION: The participants were 336 older community dwelling individuals selected from the Yale health and aging project (YHAP) of the established populations for epidemiologic study of the elderly program (EPESE).

CONTENT OF INSTRUMENT:

Frailty Domains:

- Age≥ 80 years
- Depression
- Infrequent exercise walking
- Near vision loss
- Gait and balance abnormalities
- Taking sedative medication
- Shoulder strength
- Knee strength
- Lower extremity disability

Non Frail/vigorous domains:

- Age<80 years
- No cognitive deficit
- Frequent exercise walking
- Good near vision

The participants were considered frail if they had 4 or more frailty attributes and 1or less vigorous attribute. They were considered non-frail if they had 2 or less frailty attributes and 3 or more vigorous attributes.

COMMENTS: The aim of the study was to observe relation of falls in frail population. Frail people were more to falls during the 01 year follow up period.

11.2.2 FRAILTY MEASURE(105). (1998) STRAWBRIDGE ET AL

STUDY POPULATION: The study population were part of community dwelling population from the Alameda county Study. The cohort compromised of 574 individuals of age range between 65 to 102 years. The average age was 74 years and 57% of the cohort was female.

CONTENT OF INSTRUMENT: The instrument covered four domains of frailty with a 16 item index. The domains covered were as follows

Physical functioning:

- Sudden loss of balance
- Weakness in arms
- Weakness in legs
- Dizziness when standing up quickly

Sensory problems:

- Difficulty reading a newspaper
- Difficulty in recognizing friend across the street
- Difficulty reading signs at night
- Hearing over the phone
- Hearing a normal conversation
- Hearing a conversation in a noisy room

Nutritive functioning:

- Loss of appetite
- Unexplained weight loss

Cognitive functioning:

- Difficulty paying attention
- Trouble finding the right word
- Difficulty remembering things
- Forgetting where put something

The individual item were scored as follows

Sensory items:

1. have no difficulty
2. have a little difficulty
3. Have some difficulty 4: have a great deal of difficulty.

Other items:

1. rarely or never had the problem in the last 12 months
2. sometimes had the problem
3. often had the problem
4. very often had the problem

Frailty was conceptualised as having problem in two or more functional domains.

COMMENTS:

One fourth scored as frail. The predictors in the frail population were cigarette smoking, heavy drinking, physical inactivity, depression, social isolation, fair or poor perceived health and prevalence of co-morbid conditions. It was hypothesized that if

these predictors can be addressed, onset of frailty can be delayed or avoided. The Frailty measure was used as a screening tool.

11.2.3 DAYHOFF ET AL(106). (1998)

STUDY POPULATION: A small group of 84 community dwelling participants living independently with age range of 60 to 88 years and average age of 74 years

CONTENT OF INSTRUMENT: The performance of activity of daily living as outlined in the World Health Organisation assessment of functional capacity was used. Fourteen items covering six major domains of functioning were included covering cognition, mobility, self-care, social and domestic activities and participating in community activities. Each item was scored on scale of 1 to 5 .Score of 14 or less corresponded to independence and higher score of 70 meant total dependence. Frailty was defined as a score of 21 or more.

COMMENT: Frailty was defined as disability. The study was performed as a sub-analysis of a larger study examining the effect of exercise intervention.

1. Rockwood et al(211). (1999)

STUDY POPULATION: Rockwood et al used the cohort initially compiled in the Canadian Study of Health and Aging in 1992 which comprised of 9008 community resident. In 1996-97 they contacted the surviving members to find out residential history since first contact.

CONTENT OF INSTRUMENT: The frailty scale was based on the geriatric status scale which was developed to target patients in hospital which required specialist input. The items included were scored as follow.

0. Those who walk without help, perform basic activities of daily living (eating, dressing, bathing, bed transfers),are continent of bowel and bladder, and are not cognitively impaired;

1. bladder incontinence only;

2. One (two if incontinent) or more of needing assistance with mobility or activities of daily living, has CIND, or has bowel or bladder incontinence; and

3. Two (three if incontinent) or more of totally dependent for transfers or one or more activities of daily life, incontinent of bowel and bladder, and diagnosis of dementia.

COMMENTS: The frailty scale showed a dose response relation between grades of frailty and subsequent institutionalisation and death. Frailty was defined by comorbidity and disability. Incontinence was included to see whether it was an independent marker of poor outcome.

11.2.4 MODIFIED PHYSICAL PERFORMANCE TEST(107).(2000) BROWN ET AL

STUDY POPULATION: 107 community dwelling participants with average age of 83 years age. The study was carried out in USA.

CONTENT OF INSTRUMENT: The index comprised of 9 items each being scored on scale 0 to 4.

1. Book lift. A 7-lb book is lifted from waist height to a shelf about 12 inches above shoulder level.

2. Put on and take off a coat. Subjects put on and take off a standard lab coat of appropriate size as quickly as able.

3. Pick up a penny from floor. The penny is placed about 12 inches in front of the foot on floor.

4. Chair rise. The chair is 16 inches in height. Participants are asked to sit in the chair and then get up and sit down again for 5 times.

5. Turn 360°. Participants turn both clockwise and counter clockwise quickly but safely. .

6. 50-ft. walk. Subjects walk 25 ft. in a straight line, turn, and return to the initial starting place.

7. One flight of stairs. Participants are asked to climb a fight of 10 steps.

8. Four flights of stairs. Participants climb four flights of stairs. One point is given for each flight of stairs completed.

9. Progressive Romberg test. Participants are asked to stand feet together, semi-tandem, and full tandem, for a maximum of 10 seconds.

All activities were scored on the time taken for completion. Scores ranged from 0 to 36 and frailty was graded as; dependent <17, moderately frail 17-24, mildly frail 25-32, Not frail 32-36.

COMMENT: This physical performance test only concentrates on the physical domain of frailty. There findings suggested that isolated measure of strength, flexibility and coordination were insufficient for the identification of frailty.

11.2.5 Fried Frailty Phenotype(46).(2001) Fried et al

STUDY POPULATION: The participants were originally part of cardiovascular health study (CHS) and comprised of 5317 community dwelling individuals aged 65 years or more.

CONTENT OF INSTRUMENT: The main domains used to define frailty were weight loss, feeling of exhaustion, physical activity, gait speed and hand grip strength

- Weight Loss- Unintentional loss of 10 pounds in weight over last year
- Exhaustion- Assessed by question derived from CES_D depression scale

- Physical activity-Kcal per week calculated from Minnesota Leisure Time Activity questionnaire
- Grip strength-stratified according to gender and BMI.
- Gait time-calculated for a 15 feet walk at normal walking speed.

Frailty was diagnosed if three or more criteria were present. Participants with one or two criteria were termed as pre-frail.

COMMENTS: The study aimed to provide a standardised definition of frailty in community dwelling older people. It also concluded that frailty was not synonymous with comorbidity or disability but ware an outcome of frailty.

11.2.6 GRONINGEN FRAILTY INDICATOR(108). (2001) STEVERINK ET AL

STUDY POPULATION: Study participants comprised of 275 individuals ranging from 64 to 99 years of age dwelling not only in the community but hospital inpatients and nursing home residents were also included. Average age was 78 years. It was a cross sectional study carried out in Netherlands.

CONTENT OF INTRUMENT: The 15 item index covered the domains of mobility, vision, hearing, nutrition, co-morbidity, cognition, psychosocial status and physical fitness. The contents of criteria were

Can the patient perform the following tasks without assistance from another person

1. Grocery shopping
2. Walk outside the house
3. Getting undressed
4. Visiting restroom
5. Does the patient encounter difficulties in daily life because of impaired vision?
6. Does the patient encounter problem in daily life because of impaired hearing?
7. Has patient lost weight unintentionally in past 6 months (6kg in six months or 3kg in 3 months)
8. Does the patient use 4 or more different types of medication?
9. Does the patient have any complaints about his/her memory of diagnosed with dementia?
10. Does the patient ever experience emptiness around him? e.g you feel so sad that you have no interest in your surroundings.
11. Does the patient ever miss the presence of other people around him?

12. Does the patient ever feel left alone?
13. Has the patient been feeling down or depressed lately?
14. Has the patient felt nervous or anxious lately?
15. How would the patient rate his/her own physical fitness on a scale of zero to ten?

Patient was considered frail if score was five or more with a maximum of 15.

COMMENT: The index has been validated against the frailty index and a moderate overlap was found for detecting frailty in community and it was suggested that initial screening should be with frailty index in primary care(212).

11.2.7 FRAILTY INDEX(109).(2002) MITNITSKI, ROCKWOOD ET AL

STUDY POPULATION: Secondary analysis was carries on representative cohort of the Canadian Study of health and aging (CHSA) which included 2914 participants of age 65 years and above. The average age was 82 years.

CONTENT OF INSTRUMENT: The frailty index was based on proportion of 20 deficits observed during structured clinical examination. The items included in the index were as follows

- Vision Loss
- Impaired mobility
- Gait abnormality
- Difficulty toileting
- Difficulty bathing
- Difficulty grooming
- Resting tremor
- Difficulty dressing
- Gastrointestinal problems
- Hypertension
- Hearing loss
- Vascular problem
- Impaired vibration sense
- Difficulty cooking
- Difficulty going out
- Skin problems
- Changes in sleep
- Urinary complaints
- Diabetes
- Limb tone abnormality

Each deficit was given a value of 1 if present. No clear cut-off for frailty was published. In later frailty studies on the same population Rockwood et al used a 70 item frailty index(115).

COMMENTS: Frailty index was used to estimate the accumulation of deficits with age. His was used to estimate the biological age of the participant. The average value to

frailty index increased with age in log-linear fashion. Advance biological age was significantly associated with mortality then chronological age. The average increase in frailty index amongst those without any cognitive deficit was 3 per year.

11.2.8 BINDER ET AL(110). (2002)

STUDY POPULATION: 444 community dwelling individuals were included in the study with average age of study cohort of 83 years. This is one of the few randomised controlled trial about frailty.

CONTENT OF INSTRUMENT:

- Modified Physical Performance Test- 7 standardised timed tasks including 50 feet walk, putting on and removing a lab coat, picking up a penny from floor, standing up 5 times from 16 inch chair, lifting a 7 pound book to a shelf, standing with feet in side by side, semi-tandem and full tandem position and two additional tasks (climbing up and down four flight stairs and performing a 360 degree turn.

- ADL Measures:-The Older American Resource and services (OARS) instrument was used to collect information about assistance needed to perform ADLs and IADL. Functional status questionnaire was used to collect information about difficulty in performing tasks over the last month.

- Peak Oxygen Uptake- was assessed during a graded treadmill walk test.

COMMENT: The frailty assessment tool was developed to select mild to moderate frail community dwelling participants to see if intensive exercise training can improve frailty. The physical performance of individuals improved with exercise program compared to controls in the study.

11.2.9 GILL ET AL(111, 213) (2002)

STUDY POPULATION: 188 community dwelling individuals with ages 75 years and above were evaluated with a battery of qualitative and performance tests. The average age was 83 years of age.

CONTENT OF INSTRUMENT: The test comprised of walking as fast as possible over a course of 10 feet and a single chair rise. The participants were scored as moderate frail if the gait speed was more than 10 seconds or if they could not rise from the chair. They were scored as severely frail if they failed to meet both criteria.

COMMENT: The main aim of the study was to evaluate the risk of developing dependence in activities of daily living in community dwelling older individuals with mild to moderate cognitive impairment.

11.2.10 SUBJECTIVE FRAILTY SCORE(214).(2003) GERDHEM ET AL

STUDY POPULATION: Swedish study comprising of 993 randomly selected women of 75 years in age.

CONTENT OF INSTRUMENT: A subjective end of bed assessment was used. Frailty was estimated on basis of general assessment of health and appearance within 15 seconds from first sight and transferred on to an arbitrary scale of 1 to 100. No clear cut-offs value between frail and non-frail could be found.

COMMENTS: The main objective of the study was to see if there was any correlation between frailty and bone mass density. High frailty score was significantly correlated with poor gait, poor balance, low muscle strength, low activity level and high risk of falling but bone mass could not be predicted with a subjective frailty score.

11.2.11 KLEIN FRAILTY INDEX(112)(2003) KLEIN ET AL

STUDY POPULATION: The study cohort was based on community based population sampled from private consensus of the Beaver Dam Eye study. The age ranged from 43 to 86 years of age. Over 2962 were included in the study.

CONTENT OF INSTRUMENT: A frailty index was derived of following parameters.

- Gait speed: Time taken to walk 10 foot or 3 meter. Highest quartile was taken as abnormal. >3.37 sec in women and >3.19 sec in male.
- Hand Grip test: Dominant hand. Lowest quartile was taken as abnormal which was 18.5 kg for women and 34.5 kg for men.
- Peak expiratory flow rate: less than 290 l/min in women and less than 440 l/min in male were taken as abnormal.
- Chair Stand: This was done without use of hands and scored if participant was unable to do.

The score was reported on scale of 1 to 4, four being the maximum score.

COMMENT: The main aim of the study was to assess association between frailty and visual function. A significant association was found between greater frailty and poor visual function and it was proposed that inclusion of visual function assessment may improve the usefulness of a frailty index.

11.2.12 CLINICAL GLOBAL IMPRESSION OF CHANGE IN PHYSICAL FRAILTY (CGIC-PF)(113).

STUDY POPULATION: A frailty assessment tools was developed after literature review in academic setting to cover all frailty domains. It was then conducted a very small group of participants of 11-14 people mainly to assess content validity and feasibility.

CONTENT OF INSTRUMENT:

- Appearance- Grooming, posture, personal hygiene.
- Healthcare Utilisation- hospitalisation, home care, frequency of doctor visits

- Medical Complexity- number and severity of diagnosis, stability of condition, number and complexity of medication.
- Strength-grip, chair rise, manual muscle test
- Balance-Falls, fear of falling, balance examination
- Nutrition- weight, albumin level, cholesterol level
- Stamina- self reported energy and fatigue, recent activity level
- Neuromotor- speed of movements e.g. finger/foot tapping, attention e.g. multitasking, coordination e.g. rapid alternating movements
- Mobility- walking, transfer, stairs, assistive devices
- Perceived health- patient/others opinion of health
- Activities of daily living- basic, instrumental advanced, ability to travel outside home
- Emotional status- depression, anxiety
- Social status- roles, interaction with others, life events, living situation
-

COMMENTS: Frailty assessment tools constructed to cover all domains of frailty including subjective as well as objective measures. It need a detailed interview to complete and was completed within 10 minutes during the study. No clear cut-offs for frailty scores were given.

11.2.13 EPIDOS DEPENDENCE INDEX(114). (2005) CARRIERE ET AL

STUDY POPULATION: The study sample was derived from Epidemiologie de I'Osteoporose study (EPIDOS) study. I constituted of 545 women of 75 years and above in age. The study was conducted in France.

CONTENT OF INSTRUMENT: The index comprised of

- Mobility
- Fear of falls
- Gait Speed less than 0.78 m/sec
- Time to stand in tandem position
- Timed five chair stands
- BMI
- Perceived health
- Education
- Physical activity
- Grip strength

The participants were followed up for 7 years and were assessed each year for loss of at least one activity.

COMMENTS: The study was done for epidemiological purposes. It concluded that a powerful fitting method allows establishing a hierarchy between the physical frailty components and providing a predictive score of practical value.

11.2.14 7 POINT CLINICAL FRAILTY SCALE(115).(2005) ROCKWOOD ET AL

STUDY POPULATION: Study population included 2305 older adult patients from the second stage of the Canadian Study of health and aging (CSHA II). These were the participants of initial CSHA cohort who were alive at 5 years after the initial study.

CONTENT OF INSTRUMENT: Clinical frailty scale is measure of frailty on basis of clinical judgement. It requires a detailed clinical interview which is this study was carried out as part of the Canadian health and Aging study. After the interview the frailty is scored on scale of 1 to 7 as follows

1. ***Very fit***_ robust, active, energetic, well-motivated and fit, these people exercise regularly and are in the fittest group for their age.
2. ***Well***_ without active disease, but less fit than people in category 1.
3. ***Well, with treated comorbid disease***_ disease symptoms are well controlled compared to those in category 4.
4. ***Apparently vulnerable***_ although not frankly dependant, these people commonly complain of being 'slowed up' or have disease symptoms.
5. ***Mildly frail***_ with limited dependence on others for instrumental activities of daily living
6. Moderately frail_ help is needed with both instrumental and non-instrumental activities of daily living.
7. ***Severely frail***_ completely dependent on others for the activities of daily living or terminally ill.

COMMENTS: The cohort was followed up prospectively for 5 years to look for clinical frailty scale ability to predict death and or need for institutionalisation. Each single increment rise in the CFS significantly increased the medium term risk of death i.e. 21.2% mortality risk at 70 month and 23.9% increase in need for institutionalisation. The clinical scale was also compared to 70 item frailty index and showed high reliability and co-relation.

11.2.15 STATIC/DYNAMIC FRAILTY INDEX(116). (2005) PUTS ET AL.

STUDY POPULATION: The study population was derived from Longitudinal Aging Study Amsterdam (LASA). It comprised of 1321 community dwelling individuals aged 65 years and above. The participants were assessed in two stages. Initially they were assessed with physical performance tests and in second stage they self-reported functional limitation.

CONTENT OF INSTRUMENT: Nine markers were used to constitute the frailty index.

- Body Mass index
- Cognitive function

- Self-reported auditory and visual problems
- Perlin and Schooler mastery scale
- Depressive symptoms
- Physical activity
- Peak expiratory flow
- Urinary Incontinence

Participant was considered frail if 3 or more components were present. At the second stage frailty was diagnosed if participant reported decline or functional restriction in 3 or more components.

COMMENTS: The study concluded that frailty was more strongly associated with self-reported functional decline in older people than with physical performance tasks.

11.2.16 FRAILTY STAGING SYSTEM(117).(2005) CACCIATORE ET AL.

STUDY POPULATION: The study assessed long term mortality after 12 year follow up in 120 subjects with chronic heart failure and 1139 participants without heart failure from a random sample of older population in the Campania region of Italy. The average age was 75.9 years.

CONTENT OF INSTRUMENT: The index comprised of 7 domains which were scored as 1 for loss of function and zero if function was intact. The domains were

- Cognition Function
- Mobility (ability to do house work, climb single flight of stairs and walk half a mile)
- Visual function
- Hearing function
- Urine Incontinence
- Social support.
- Basic activities of daily living (BADL)

The score was divided into three classes. Class 1 included score of 0 or 1 and indicated fit people. Class2 was scored as 2 to3 while Class 3 was given to score of 4 or more.

COMMENTS: The study was done to assess the effect of frailty on long-term mortality of patients with chronic heart failure. It was found that mortality increases with frailty in older adult patient both with and without chronic heart failure. At 9 years the probability of survival progressively decreased as frailty increased (45.5% to 0%) in subjects with heart failure and 62.8% to 25.9% in subjects without heart failure.

11.2.17 EDMONTON FRAILTY SCALE(118).(2006) ROLFSON ET AL

STUDY POPULATION: The study group were a cross section of patients referred for comprehensive geriatric assessment. The participants were older adults more than65 year of age recruited from different departments in the hospital.

CONTENT OF INSTRUMENT:

- Cognition-labelling a clock face
- General health status –self reported
- Functional dependence- help with meal preparation, shopping, transportation, telephone, housekeeping, laundry, managing money, taking medication
- Social Support- self reported
- Continence
- Number of medication
- Nutrition- self reported weight loss
- Functional performance- Time get up and go test
- Mood

The maximum score was 17 with frailty graded as mild moderate and sever as per score.

COMMENTS: The main aim of the study was to develop a frailty assessment tool that can be used in routine practice and covers major domains of frailty. It is among few frailty assessment tools that objectively assesses cognition rather than self-reported memory problem.

11.2.18 SHORT PHYSICAL PERFORMANCE BATTERY (SPPB)(119). (2006) BANDINELLI ET AL

STUDY POPULATION: The participants were part of the Frailty Screening and Intervention trial (FRAISI) trial. The total number of participants was 251 which were community based , with average age of 76.4 years. The SPPB in itself was initially proposed by Guralnik et al in 1995(215). It is initially constructed to assess lower extremity dysfunction as a predictor of subsequent disability in older people.

CONTENT OF INSTRUMENT: Frailty was recorded on basis of ability of perform physical tasks.

1. Balance Tests
    a. Stand with feet together
    b. Semi-tandem stand
    c. Tandem stand
2. Gait Speed Test- 4 meter walk with two attempts
3. Chair Stand test- Five attempts timed.

All the items were scored on scale of four with a maximum score of 12. Participants scoring less than 9 were considered frail.

COMMENTS: The study interpreted frailty as disability. The main aim was to screen older adults for functional impairment so they can be involved in intensive medical and exercise intervention in a hope to prevent future disability.

11.2.19 MARIGLIANO-CACCIAFESTA POLYPATHOLOGICAL SCALE(216).(2008) AMICI ET AL

STUDY POPULATION: Italian study on a cohort of 180 older subjects with age 70 years and over. The mean age was 79.5 years.

CONTENT OF INSTRUMENT: Frailty was defined as comorbidity on this scale which comprised of a 53 item index covering comorbidities across 11 domains.

- Cardiovascular disorders (4 items)
- Respiratory disorders (5 items)
- Renal disorders (4 items)
- Metabolism and Nutrition (5 items)
- Locomotor system disorders (5 items)
- Sensory loss (5 items)
- Peripheral vascular disease (5 items)
- Malignancy disorders(5 items)
- Neurological disorders(5 items)
- Gastroenterological disorders(5 items)
- Cognitive state and mood(5 items)

The polypathology was scored on a scale of 0 to 245

Mild: Less than 15

Moderate: 15 to 24

Moderate to Severe: 25 to 49

Severe: 50 to 74

Very Severe: 75 and above

COMMENTS: The main aim of the study was to establish a method for early detection of frailty in older adult population. The study subjects were also assessed with Barthel index, global evaluation functional index, geriatric depression scale, mini mental and nutritional scale and Tinetti test, and a strong correlation was found between Marigliano-cacciafesta polypathological scale and nutritional state, mood level, mobility, disability and global functioning.

11.2.20 STUDY OF OSTEOPOROTIC FRACTURES INDEX (SOF)(217).ENSRUD ET AL.

STUDY POPULATION: The study cohort comprised of 6701 community dwelling women aged 69 years and above.

CONTENT OF INSTRUMENT: The SOF index was a simplified frailty index to make it suitable for use in clinical practice.

- Unintentional weight loss (≥5% in 2 years)
- Inability to rise from chair five times unassisted without using arms.
- Reduced energy level (Geriatric Depression Scale)

Patient was considered with score of 2 or more and pre-frail with score of 1.

COMMENTS: The SOF index was validated against a more detailed cardiovascular health study (CHS) Index. It was able to predict risk of falls, disability, fracture, and death in older women as well as the CHS index.

11.2.21 HRCA VULNERABILITY INDEX/ VULNERABLE ELDERS SURVEY(121).(2008) KANAUCHI ET AL.

STUDY POPULATION: 101 study participants who were admitted with cardiovascular risk factors. The age range was 65 to 85 years, with mean age of 72.9 years. The study was carried out in Japan.

CONTENT OF INSTRUMENT: Frailty was assessed using two indices, The Herbew Rehabilitation Centre for Aged (HRCA) Vulnerability index and the Vulnerable Elder Survey Index (VES-13). The component of the index were as follows

HRCA Vulnerability Index has two components

COMPONENT A: Needing help with

- Preparing meals
- Doing chores around the house
- Taking out garbage
- Walking up and downstairs
- Using walking stick
- Needing to use a walker
- Recall present year correctly

COMPONENT B: self-reported answers for

- Needing help leaving their residence.
- Needing help in dressing
- Having health related conditions.

Vulnerable if A component score is more than one or A component score is equal to one and B component score is zero.

VES-13 index comprised of 13 items

Physical components: Difficulty in

- Stooping, crouching kneeling.
- Lifting, carrying 10 pound heavy object
- Reaching, extending arm above shoulder level
- Writing, or handling and grasping small objects
- Walk a quarter of mile
- Heavy housework such as scrubbing floors or washing windows.

Activity components: Difficulty because of physical health

- Shopping for personal items.
- Managing money
- Walking across room
- Doing light housework

Bathing or showering

Age: 1 point for age 75-84. 3 points for age ≥85

Self-reported health compared to people of one's age

Participants were considered frail score more than 3.

COMMENTS: The study concluded that frail older adults had a significant lower quality of life and lower mental wellbeing independent of age, diabetes, microvascular complication, chronic kidney disease and depressed mood.

11.2.22 TILBURG FRAILTY INDICATOR (TFI)(122).(2010) GOBBENS ET AL

STUDY POPULATION: Two samples of 245 and 234 community dwelling participants were included with an average age of 80.3 years. The study was conducted in Netherlands.

CONTENT OF INSTRUMENT: The frailty indicator covered three main frailty domains including physical, psychological and social parameters. The index comprised of 15 items in total

Physical components:

- Perception of physical health
- Unexplained weight loss (6 kg in six months or 3 kg in last month)
- Experience difficulty in daily life due to mobility problems

Psychological components:

- Do you have problem with your memory?
- Have you felt down during the last month?
- Have you felt nervous or anxious during the last month?

- Experience difficulty in daily life due to Balance problems
- Experience difficulty in daily life due to hearing problems
- Experience difficulty in daily life due to vision impairment
- Experience difficulty in daily life due to lack of strength in hands
- Experience difficulty in daily life due to physical tiredness
- Are you able to cope with problems well?

Social components

- Do you live alone?
- Do you sometimes miss having people around you?
- Do you receive enough support from other people?

The score ranged from 1 to 15 but no clear cut offs for frailty were proposed.

COMMENTS: The TFI showed good retest reliability at 01 year: 0.79 for frailty and 0.67 to 0.78 for its domains. The indicator was validated against a number of scales representing components of each domain.

11.2.23 FRAIL SCALE(123). (2010) HYDE ET AL

STUDY POPULATION: The study cohort comprised of 3616 community dwelling men of age 71 years and above. It was a cross sectional study.

CONTENT OF INSTRUMENT:

- **F**atigue-(Short survey form SF-36)
- **R**esistance-ability to climb single flight of stairs. (SF-36)
- **A**mbulation-ability to walk one block.(SF-36)
- **I**llness-more than 5 illness out of 14
- **L**oss of weight-more than 5% between 4-5 years.

COMMENTS: The main aim of the study was to see any relation of frailty with serum testosterone level in males for which an independent association was found.

11.2.24 BRIEF FRAILTY INDEX (BFI)(124). FREIHEIT ET AL.

STUDY POPULATION: The study participants were 374 patients aged 60 and over undergoing cardiac catheterisation for coronary artery disease. The study was conducted on hospital based cohort. This was a sub study of Calgary Cardiac and Cognition Study.

CONTENT OF INSTRUMENT: The index was comprised of 5 components

- Poor balance
- Abnormal BMI

- Gait speed.
- Depressive symptoms
- Living alone

COMMENTS: The brief frailty index was found to be predictive of increased disability and decrease quality of life at 01 year. Frailty was regarded as disability.

11.2.25 OPASICH ET AL(125). (2010)

STUDY POPULATION: The study comprised of 224 patients, aged 70-87 years, who were post cardiac surgery in hospital. The study was conducted in Italy.

CONTENT OF INSTRUMENT: The study performed Balance performance oriented mobility assessment (BPOMA) and get go and go test to classify patients as frail.

- BPOMA- Performance was tested for sitting balance, attempting to rise, rising, immediate standing balance, standing balance, nudge, closed eyes, turn 360 degree and sitting down
- Get-Up-and-Go test- Time taken to walk for 5 meter ahead with patient starting from a sitting position.

The participants were grade as moderately frail (BPOMA≤19 or GUG>10sec), severely frail (BPOMA≤19 and GUG>10sec) and non-frail (BPOMA>19 and GUG≤10 sec)

COMMENTS: The patients identified as frail were subjected to a personalised physiotherapy program to enhance independent mobility

11.2.26 COMPREHENSIVE ASSESSMENT OF FRAILTY (CAF)(85). SUNDERMANN ET AL (2011)

STUDY POPULATION: The study cohort comprised of 400 patients undergoing cardiac surgery age 74 years and above. This was a hospital based study with patients having established underlying coronary artery disease.

CONTENT OF INSTRUMENT:

Modified Fried phenotype

- BMI
- Physical activity score
- Exhaustion questionnaire
- Gait speed
- Grip strength

Laboratory tests

- Serum Albumin level
- Forced expiratory volume in 1 sec.(FEV1)
- Creatinine level
- BNP

Physical performance test

- Standing balance
- Chair rise
- Put on and remove the jacket
- Pickup pen from floor
- 360 degree turn

Clinical Frailty Scale Score graded 1-7

An overall score of more than 25 was considered as frail.

COMMENTS: The main aim of the study was to develop a frailty assessment tool that can be used to assess older patients undergoing cardiac surgery or transcatheter aortic valve replacement. It was suggested to combine frailty assessment with convention risk assessment undertaken before cardiac surgery.

11.2.27 SHARE-FI (2010)-ROMERO ET AL(126)

STUDY POPULATION: The study participants were from community based cohort of Survey of Health, Aging and retirement in Europe (SHARE) project. The cohort of 15,578 individuals was assessed for frailty on basis of five frailty indicator tool, the SHARE frailty index.

CONTENT OF INSTRUMENT:

- Exhaustion: In the last month, have you had too little energy to do the things you wanted to do?
- Slowness: Because of a health problem, do you have difficulty walking 100 metres?" or "... climbing one flight of stairs without resting?
- Weight loss: What has your appetite been like? Have you been eating more or less than usual?
- Low activity: How often do you engage in activities that require a low or moderate level of energy such as gardening, cleaning the car, or doing a walk?
- Weakness: assessed by handgrip

COMMENTS: This frailty index was based on frailty phenotype suggested by Fried et al and the main aim was to provide as alternative valid to European population.

12 ABBREVIATIONS:

ACS	Acute coronary syndrome
ACUITY	Acute Catheterisation and urgent intervention strategy
AE	Adverse effect
AF	Atrial Fibrillation
AIDS	Acquired immunodeficiency Syndrome
AKI	Acute Kidney Injury
ANOVA	Analysis of variance
AR	Adverse reaction
AUC	Area under curve
BADL	Basic activities of daily living
BARC	Bleeding Academic Research Consortium
BCIS	British Cardiovascular Intervention Society
BCP	Blood chemical profile
BCP	Blood chemical profile
BMI	Body mass index
BNP	Brain natriuretic factor
CABG	Coronary artery bypass grafting
CAF	Comprehensive assessment of frailty
CCS	Canadian Cardiovascular Society
CD	cluster of differentiation
CES-D	Centre of epidemiological studies depression scale
CI	Confidence Interval
CIRS	Cumulative Illness rating scale
Cr	Creatinine
CRP	C Reactive Protein
CRT-D	Cardiac resynchronisation Therapy- Defibrillator
CRUSADE	can rapid risk stratification of unstable Angina Patients Suppress Adverse Outcomes With Early Implementation Of The ACC/AHA Guidelines
CSHA-FS	Canadian Study of Health and Aging-Clinical Frailty Scale
CT	Computer Tomography
cTn	Cardiac troponin
CVA	Cerebrovascular accident
CVD	Cardiovascular Disease
CXC	Chemokine
DHEA	Dihydroepiandesterone
EC	Ethics Committee
ECG	Electrocardiogram
ECG	Electrocardiogram
EENT	Eyes, ear, nose and throat
eFI	Electronic frailty index
EFS	Edmonton frailty scale
eGFR	Electronic glomerular filtration rate
EUROSCORE	European System for Cardiac Operative Risk Evaluation

FBC	Full blood count
FBC	Full blood count
FFP	Fried frailty phenotype
FORECAST	Focal Recurrent Assessment and Salvage Treatment
GCP	Good Clinical Practice
GI	Gastrointestinal
GRACE	Global registry of acute cardiac events
GU	Genitourinary
GUSTO	The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries
Hb	Haemoglobin
HEY	Hull and East Yorkshire
HF	Heart failure
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
HS-CRP	High sensitivity C reactive protein
IADL	Instrumental activities of daily living
ICD	Internal defibrillator device
IGF	Insulin like growth factor
IL	Interleukin
Kcal	Kilocalories
KCCQ	Kansas city cardiomyopathy questionnaire
LAD	Left Anterior Descending
LBBB	Left Bundle Branch Block
LCX	Left Circumflex
LFT	Liver function test
LIMA	Left Internal Mammary artery
LMS	Left main stem
LV	Left Ventricle
MACE	Major Adverse Clinical Event
MACE	Major adverse clinical event
MCS	Mental composite score
MI	Myocardial infarction
MINAP	Myocardial Ischaemia National Audit Project
MMSE	Mini-mental scale examination
MRI	Magnetic Resonance Imaging
NRMI	National registry of Myocardial Infarction
NSTEMI	Non ST elevation myocardial infarction
NSTEMI	Non ST elevation myocardial infarction
NT-proBNP	N-terminal pro-Brain Natriuretic Peptide
NYHA	New York Heart Association
OPERA-HF	Observational study to assess and Predict the in-patient course, risk of Re-Admission and mortality for patients hospitalised for or with Heart Failure
PARTNER	Placement of Aortic Trans catheter Valves
PASPr	Pulmonary Artery Systolic Pressure

PCI	Percutaneous coronary intervention
PCS	Physical composite score
PPM	permanent pacemaker
QoL	Quality of life
R& D	Research and development
RCA	Right coronary artery
RCT	randomised control trial
REC	Research ethic committee
RIMA	Right Internal mammary artery
RINCAL	Revascularisation or medical therapy in elderly patients with acute angina syndromes.
ROC	Receiver operator curve
SA	Stable Angina
SAE	Serious adverse effect
SD	Standard deviation
SE	Standard Error
SENIOR-RITA	The British Heart Foundation older patients with non-ST Segment elevation Myocardial Infarction Randomised Interventional Treatment Trial
SF	Short Form
SPSS	Statistical package for social sciences
STEMI	ST elevation myocardial infarction
STS	Society of thoracic surgeons
SVG	Saphenous venous graft
SYNTAX	Synergy between PCI with Taxus and Cardiac Surgery
TACTICS_TIMI	Treat angina with Aggrastat and determine Cost of Therapy with an Invasive Strategy-Thrombolysis in Myocardial Infarction
TAVR	Trans-aortic valve replacement
TIA	Transient ischemic attack
TIME	Trial of invasive versus medical therapy in elderly patients with chronic symptomatic coronary-artery disease
TNF	Tissue necrosis factor
U&E	Urea and electrolyte
UK	United kingdom
URL	Upper range limit
USA	Unstable Angina
VIGOUR	Virtual Coordinating Centre for Global Collaborative Cardiovascular Research
Yrs	Years