GSC Biological and Pharmaceutical Sciences

eISSN: 2581-3250 CODEN (USA): GBPSC2

Cross Ref DOI: 10.30574/gscbps

Journal homepage: https://gsconlinepress.com/journals/gscbps/

(RESEARCH ARTICLE)

Pre-morbid frailty is associated with poor outcome after thrombolysis in older patients with ST-elevation Myocardial Infarction

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GSC Biological and Pharmaceutical Sciences, 2023, 24(01), 263–272

Publication history: Received on 29 May 2023; revised on 17 July 2023; accepted on 19 July 2023

Article DOI: https://doi.org/10.30574/gscbps.2023.24.1.0282

Abstract

Introduction: In recent years, the association of frailty has been established with a poor outcome after percutaneous intervention following an acute cardiovascular event. However, a larger proportion of the world population is unable to access the prohibitively expensive tertiary cardiac care and receives the more readily available, affordable and acceptable thrombolytic therapy in emergency situations. The current study was designed to explore the association of pre-morbid frailty with immediate and short-term outcome of thrombolysis in older subjects presenting with ST-elevation myocardial infarction to our hospital.

Methods: This was an observational prospective cohort study completed between 2015 and 2017 at a tertiary care teaching hospital in Delhi. Patients older than 60 years who presented to the hospital with ST-elevation myocardial infarction and underwent successful thrombolysis were included for the study. Complications such as bleeding, reperfusion reactions and allergic reactions were recorded whenever these were observed. In addition, complications such as re-infarction, stroke, cardiac arrest, cardiogenic shock and death were also recorded. In addition, a short-term outcome in terms of discharge, death, recovery was noted.

A pre-morbid frailty score was historically computed with inputs from the patients and their primary caretakers using a deficit count approach on a pre-defined list of fifty self-reported deficits.

The descriptive statistical analysis comprised of calculating means (standard deviations) and proportions (frequencies and percentages). The association of premorbid deficit score with thrombolysis success and other variables was tested by calculating mean ranks, and Mann Whitney U test was used as a statistical test of significance. Spearman correlation coefficient was used to determine the association between frailty and complications and morbidity and mortality indicators. Univariable logistic regression models were used to evaluate independent variables associated with outcome of thrombolysis to further explore the association between frailty and outcome. Independent variables found significantly associated with poor outcome were entered into a multivariable logistic regression model (forward) in addition to those considered scientifically relevant.

Results: In the present study, we found a significant association between a higher pre-morbid frailty status assessed by an interview-based deficit count score and poorer outcome of thrombolysis. Every unit increment in the frailty deficit count score on a scale of 50 points increased the odds of failed thrombolysis by 1.14 times. Frailty was also associated with an increased risk of reperfusion arrhythmias and cardiac arrest following thrombolysis. Additionally, we noted that higher the deficit score, lesser the resolution of ST segment on ECG, 90 minutes following thrombolysis.

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Conclusions: Our study indicates that frailty determined by a premorbid count of health deficits is associated with the outcome of thrombolysis following myocardial infarction in older patients. The patients with greater count of deficits have a higher chance of failure. Our findings will help informed decision-making while managing older patients presenting with myocardial infarction and in-turn improve morbidity and mortality.

Keywords: Coronary Artery disease; Myocardial infarction; Frailty; Coronary heart disease

1. Introduction

Frailty is a physiological syndrome characterized by decreased reserve and diminished resistance to stressors, resulting from cumulative decline across multiple physiological systems and causing vulnerability to adverse outcomes.[1] It is manifested as loss of skeletal muscle mass (sarcopenia), abnormal function in inflammatory and neuroendocrine systems, and reduced energy regulation. The overall health and prognosis of the older adults are influenced by frailty, co morbid conditions, general health status along with the status of cardiovascular health. It is interesting to note that the current guidelines by the American College of Cardiology/American Heart Association (ACC/AHA) underscore the need to assess general health, co morbidity, cognitive status, and life expectancy[2,3] but surprisingly do not mention frailty, despite the fact that it is common in older persons presenting with cardiovascular disease (CVD).[2,4]

The prevalence of *physical frailty* has been recorded at 10% and nearly 14% individuals have been found to fulfil the broader frailty phenotype.[5] In fact, subjects with heart disease have been found to have a higher prevalence of frailty as compared to those without CVD.[6] Further, the reported frailty in patients aged ≥65 years undergoing PCI is 20%.[7]

Cardiovascular diseases are an important cause of morbidity and mortality among older persons. Currently, around 4.1 million die from CVD every year, and it has been shown that 82% of them are older than 65 years, while 46% were over 75 years of age.[8] Further, it has been established that approximately 60-65% of ST-elevation myocardial infarctions (STEMI) occur in the patients of more than or equal to 50 years of age, with 11% in those over 75 years.[9] Furthermore, 80% of deaths due to STEMI occur in patients more than or equal to 65 years of age. The older person continues to remain at a higher risk for morbidity and mortality from cardiovascular disease, and many studies have provided insight into risks and benefits in this age group.[10,11]

Primary percutaneous intervention (PPCI) remains the treatment of choice for STEMI when it can be performed rapidly. It being resource intensive, is available in only about 37 percent of all acute care, adult hospitals in the United States.[12] Thus, all STEMI patients who cannot receive PPCI in a timely manner due to geographical or logistic constraints should be considered immediately for fibrinolytic therapy. While recent studies have explored the relationship between frailty and percutaneous intervention and frailty in older persons with CVD, there is limited guidance on whether and how metrics of frailty should be applied to influence risk–benefit decision-making for utilization of these interventions.[13]

The current study was designed to explore the association of pre-morbid frailty with immediate and short-term outcome of thrombolysis in older subjects presenting with ST-elevation myocardial infarction to our hospital.

2. Methods

This was an observational prospective cohort study completed between 2015 and 2017 at a tertiary care teaching hospital in Delhi. The study was initiated after approval by the Institutional Ethics Committee for Human Research at our college and patients were included after they provided a written and informed consent.

Patients older than 60 years who presented to our hospital with ST-elevation myocardial infarction and underwent successful thrombolysis, based on ACCF/ AHA guidelines were included for the study. [14] Successful thrombolysis was defined by at least 50% settlement of elevated ST-segment in an electrocardiogram taken after ninety minutes of initiation of thrombolysis.[15] Complications such as bleeding, reperfusion reactions and allergic reactions were recorded whenever these were observed. In additions, complications such as re-infarction, stroke, cardiac arrest, cardiogenic shock and death were also recorded.[16-18] In addition, a short-term outcome in terms of discharge, death, recovery was noted.

Any complication occurring during or after the procedure was recorded and managed appropriately. A pre-morbid frailty score was historically computed with inputs from the patients and their primary caretakers using a deficit count approach on a pre-defined list of fifty self-reported deficits.[19,20] Deficits were classified into comorbidities (14), disability (13), dependence (13) and psycho-social (13) domains. A detailed list of deficits is provided in annexure I.

The data was analyzed using Stata (Version 13, Stata Inc, USA) software. The descriptive statistical analysis comprised of calculating means (standard deviations) and proportions (frequencies and percentages). The association of premorbid deficit score with thrombolysis success and other variables was tested by calculating mean ranks, and Mann Whitney U test was used as a statistical test of significance. Spearman correlation coefficient was used to determine the association between frailty and complications and morbidity and mortality indicators. Univariable logistic regression models were used to evaluate independent variables associated with outcome of thrombolysis to further explore the association between frailty and outcome. Independent variables found significantly associated with poor outcome were entered into a multivariable logistic regression model (forwards) in addition to those considered scientifically relevant.

3. Results

3.1. Baseline parameters of participants

A total of one hundred patients who presented to our hospital with myocardial infarction were included in the study. The mean age of the participants was 67.4 (±17) years and there were 40 (40%) females. Following thrombolysis, 62 (62%) patients had successful resolution in the ST-segment elevation. The baseline comparison of the study participants is presented in **table 1**.

Table 1 The baseline comparison of the study participants

Variable	Successful thrombolysis	Thrombolysis failure	P	Total population
Total numbers	62	38	0.11	100
Age	67.2 (8.2)	68 (9.2)	0.6	67.49(8.5)
Sex (Male)	41 (66.1%)	19(50%)		
Door to needle time	53.5 (43.9)	39.3 (39.3)	0.1	48.09(42.5)
Systolic blood pressure	126.8 (27.1)	123.9 (34.3)	0.6	125.68 (29.9)
Diastolic blood pressure	76.4 (17.3)	74.4 (20.9)	0.6	76.64(18.6)
Days in hospital	0.4 (1.4)	1.6 (4.1)	0.03	0.84(2.7)
Pill burden**	1.1 (1.8)	2.4 (2.8)	<0.01	1.58(2.3)
Serum Sodium (meq/L)**	140.1 (3.9)	137.5 (5.9)	<0.01	139.14(4.9)
Serum Potassium (meq/L)	4.2 (0.6)	4.3 (0.6)	0.6	4.27(0.6)
Respiratory rate (per minute)*	15.2(2.4)	16.4(3.0)	0.03	15.7(2.7)
Pulse*(per minute)	87.7(16.3)	95.9(22.1)	0.04	90.8(19.0)
Hemoglobin (mg/dl)	12.2(1.7)	12.2(1.8)	0.9	12.1(1.7)
Random blood sugar (mg/dl)	159.0(78.1)	168.7(84.3)	0.6	162.7(80.2)
Serum Urea (mg/dl)	38.1(14.6)	44.8(24.4)	0.1	40.6(19.1)
Chest pain	58 (93.5)	34 (89.4)	0.46	92
Dyspnoea	30(48.3)	19(50)	0.87	49
Syncope	6(9.6)	4(10.5)	0.89	10
Shoulder pain	18(29.0)	14(36.8)	0.41	32
Back pain	19(30.6)	10(26.3)	0.64	29
Fatigue	6(9.6)	5(13.1)	0.58	11
Confusion*	1(1.6)	5(13.1)	0.01	6
Epicardial pain	8(12.9)	6(15.7)	0.68	14

Bleeding*	4(6.4)	9(23.6)	0.01	13
Reperfusion arrhythmias	4(6.4)	3(7.8)	0.78	7
Allergy	2(3.2)	0(0.0)	0.26	2
Reinfarct	3(4.8)	2(5.2)	0.92	5
Stroke	2(3.2)	1(2.6)	0.86	3
Cardiogenic shock**	13(20.9)	21(55.2)	<0.01	34
Death	0(0.0)	2(5.2)	0.06	2
Pallor	6(9.6)	4(10.5)	0.89	10
Edema	1(1.6)	0(0.0)	0.43	1
Chronic obstructive pulmonary disease	13(20.9)	11(28.9)	0.36	24
Coronary artery disease	13(20.9)	11(28.9)	0.36	24
Congestive heart failure	3(4.8)	3(7.8)	0.53	6
Arthritis	25(40.3)	21(55.2)	0.14	46
DM	20(32.2)	14(36.8)	0.63	34
Hypertension	30(48.3)	21(55.2)	0.50	51
Chronic kidney disease	1(1.6)	1(2.6)	0.72	2
Cerebrovascular accident	1(1.6)	2(5.2)	0.29	3
Malignancy	0(0.0)	1(2.63)	0.19	1
Toilet	3(4.8)	5(13.1)	0.13	8
Bathing	0(0.0)	2(5.2)	0.06	2
Dressing	1(1.6)	3(7.8)	0.12	4
Chair in	2(3.2)	4(10.5)	0.13	6
Grooming	0(0.0)	2(5.2)	0.06	2
Feeding	1(1.6)	0(0.0)	0.43	1
Walk house	3(4.8)	6(15.7)	0.06	9
Stairs*	7(11.2)	12(31.5)	0.01	19
Shopping	7(11.2)	7(18.4)	0.31	14
Phone use**	31(50.0)	29(76.3)	<0.01	60
Medication*	2(3.2)	7(18.4)	0.01	9
Out alone	6(9.6)	8(21.0)	0.11	14
Stay in bed	6(9.6)	9(23.6)	0.05	15
Tremor	3(4.8)	6(15.7)	0.06	9
Low food intake*	12(19.3)	16(42.1)	0.01	28
Hear Difficulty	18(29.0)	11(28.9)	0.99	29
Vision Difficulty	39(62.9)	30(78.9)	0.09	69
Vertigo	10(16.1)	8(21.0)	0.53	18
Gait imbalance	4(6.4)	2(5.2)	0.80	6

Urinary incontinence	5(8.0)	6(15.7)	0.23	11
Smoking	26(41.9)	20(52.6)	0.29	46
Alcohol use	4(6.4)	2(5.2)	0.80	6
Oral tobacco*	12(19.3)	2(5.2)	0.04	14
Depression	3(4.8)	5(13.1)	0.13	8
Everything effort	5(8.0)	8(21.0)	0.06	13
Lonely	5(8.0)	6(15.7)	0.23	11
Tired all time*	8(12.9)	11(28.9)	0.04	19
Bereavement	6(9.6)	5(13.1)	0.58	11
Weight loss	8(12.9)	9(23.6)	0.16	17
Fall	10(16.1)	5(13.1)	0.68	15

Results are presented as mean (+SD) or as number (percent) as applicable; * indicates that the difference between groups is statistically significant ($p<0.05$); ** indicates that the difference between groups is very statistically significant ($p<0.01$)

3.2. Assessment of frailty

A count on a pre-defined list of health-deficits was calculated for each patient and a negatively scaled score (0-50) was assigned based on the number of deficits. The median deficit count was 9 (IQR; 6, 13). Chronic obstructive airway disease and previous coronary artery disease were the most common comorbidity deficits found and were seen in 24 patients. A frequency histogram of deficit counts in the study subjects, differentiated by outcome of thrombolysis, is shown in figure 1.

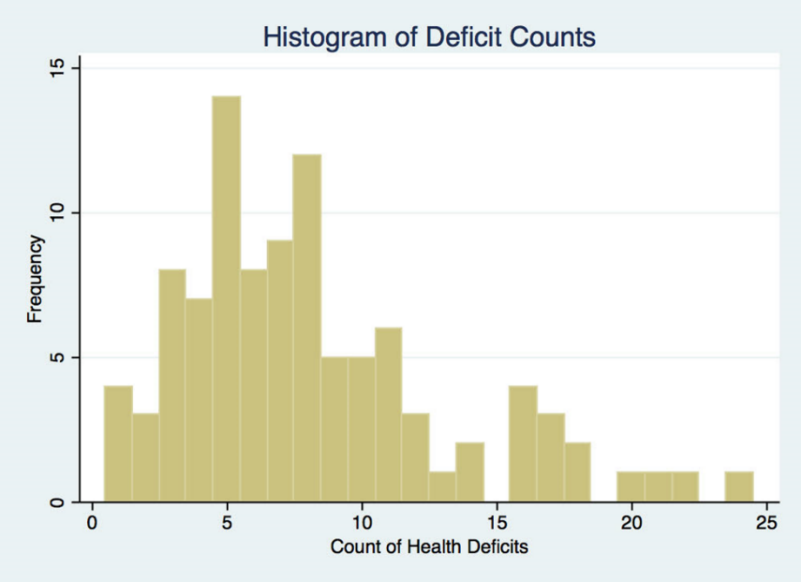

Figure 1 Histogram of deficit counts

The most common deficits observed in our participants were hypertension and arthralgia among comorbidities; needing assistance in activities of daily living (using phone, shopping); difficulty in chewing food and vision; smoking or widowed status.

3.3. Outcome and complications

An association was found between the count of pre-morbid deficits observed in the patients and failure of thrombosis. Those who had failed thrombosis had a significantly higher count than those who had successful thrombosis. A box plot showing the difference in deficit count is presented in **figure 2**.

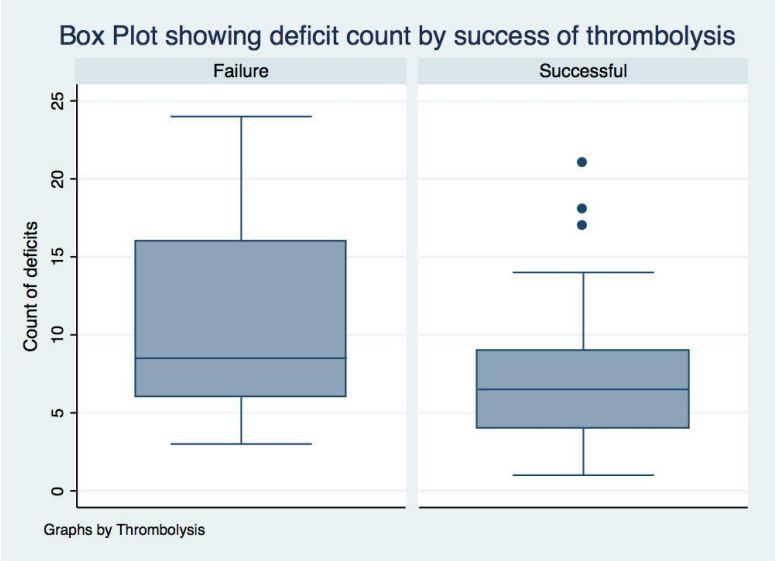

Figure 2 Box plot showing deficit count by success of thrombolysis

A significant correlation was found between the count of deficits and percentage resolution of ST segment elevation (r, -0.249; p, 0.01). A scatter diagram for this association is presented in **figure 3**.

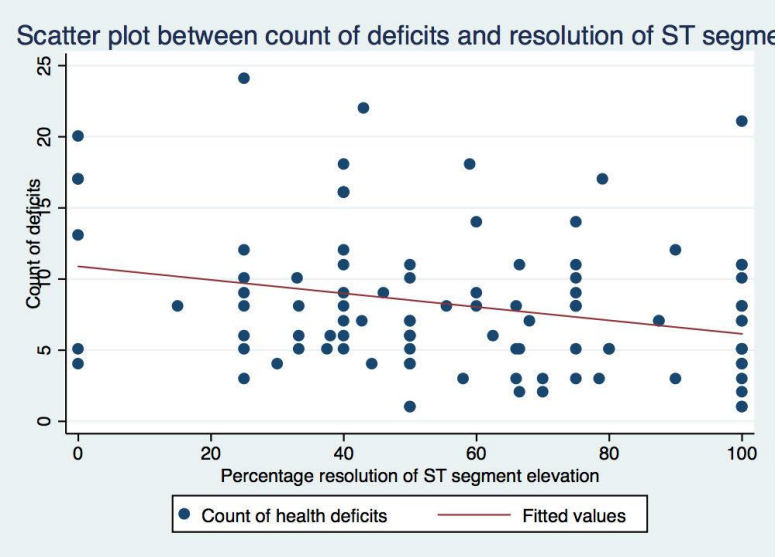

Figure 3 Scatter plot between count of deficits and resolution of ST segme

Cardiogenic shock was seen in 34 (34%) patients and bleeding in 13 (13%). In addition, reperfusion injury (n, 7; 7%), re-infarction (n, 5; 5%), and stroke (n, 3; 3%), were also noted. Two patients had allergic reactions and two died during the study period.

Table 2 Logistic regression analysis for successful thrombolysis

	Crude OR (p value)	**Adjusted OR (p value)**
Age	0.99 (0.94, 1.03)	1.0 (0.95, 1.05)
Sex	1.95 (0.86, 4.46)	1.57 (0.65, 3.77)
Count	0.87 (0.79, 0.95)*	0.88 (0.8, 0.96)*

A logistic regression model was developed using successful thrombolysis as the dependent variable to explore the association between the pre-morbid frailty state (defined by count of deficits) and other independent variables. Parameters were included if they made clinical sense and/or were found significantly associated with the outcome. The results of multivariable logistic regression analysis are presented in **table 2**.

It is seen that after adjusting for age, sex in a multivariable logistic regression analysis an increase in the number of deficits is significantly associated with increased odds for a failed thrombolysis.

A receiver operator characteristic (ROC) curve to identify best cut-off scores for the count of deficits to predict outcome returns an area under the curve (AUC) of 0.67 (95% CI; 0.57, 0.78) is presented in **figure 4**. A count of more than 8 deficits gives a sensitivity of 0.61 and a specificity of 0.61

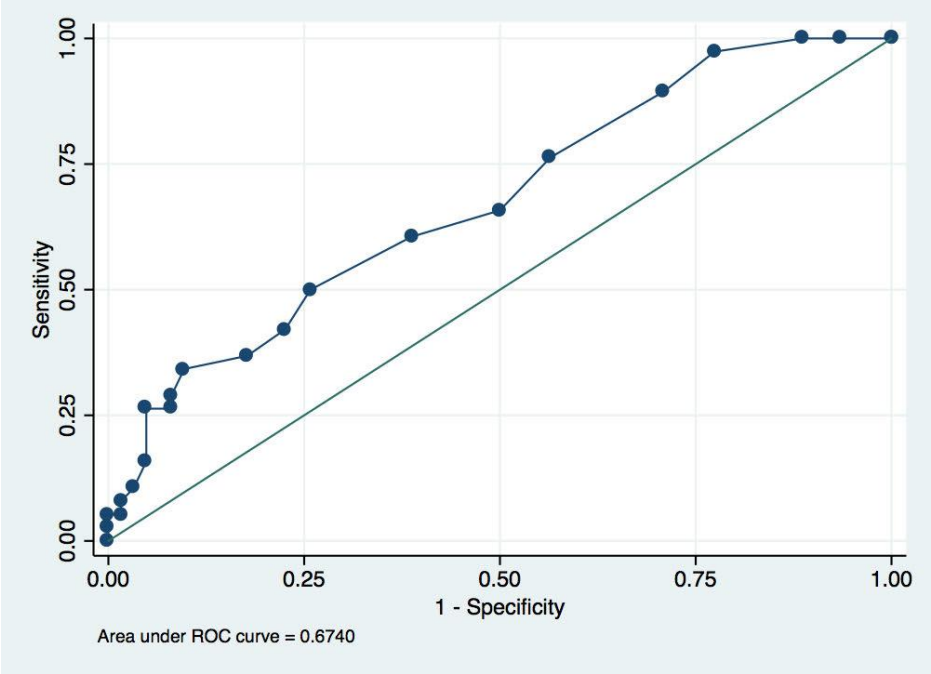

Figure 4 Receiver operator characteristic (ROC) curve for the count of deficits as predictor for successful thrombolysis

4. Discussion

In the present study, we found a significant association between a higher pre-morbid frailty status assessed by an interview-based deficit count score and poorer outcome of thrombolysis. Every unit increment in the frailty deficit count score on a scale of 50 points increased the odds of failed thrombolysis by 1.14 times. Frailty was also associated with an increased risk of reperfusion arrhythmias and cardiac arrest following thrombolysis. Additionally, we noted that higher the deficit score, lesser the resolution of ST segment on ECG, 90 minutes following thrombolysis.

In a recent publication, Dou et al have systematically reviewed 15 studies and reported a pooled relative risk of 1.54 prompting the authors to suggest that frailty should be included in risk assessment for informed decision-making algorithms for patients presenting with acute coronary syndrome.[21] Similar results have been reported by other researchers in recent times.[22,23] A review of individual studies reveals a considerably older subject base and fewer focused on patients with STEMI.[24] Further, the analysis did not consider attention to therapy but focused on the outcome in terms of mortality following the event, although the authors did suggest benefit in favor of PCI over thrombolysis in frail subjects with STEMI due to a higher risk of re-bleeding and complications. These suggestions in their meta-analysis were largely informed by a previous analysis by Sujino et al who had retrospectively studied short-term in-hospital mortality in 62 elderly patients (>85 years) with STEMI and concluded that low albumin, increased BMI, higher troponin I and frailty (CHS score) were poor prognostic indicators.[24] However, authors again did not address the nature of therapy provided to their participants.

Studies exploring the association between frailty and acute coronary syndromes have considerable heterogeneity not only in terms of age of participants but also the frailty tool used for assessment. While some studies include very old patients,[24,25] others have a considerably younger subject selection criteria[26] making generalization difficult and confusing. Further diversity exists in the inclusion across a wide spectrum of acute coronary syndrome. While some authors have included type 1 myocardial infarction,[27] only Sujino et al have studied STEMI.[24] Moreover, it is important to note that most studies have assessed frailty at or after presentation,[25,27] and even at discharge.[26,28] Frailty assessment made after an acute event is would inherently be biased by the severity of disease. However, Kang et al have reported frailty to be associated with mortality independent of disease severeity.[29]

Our study attempts to look at a cohesive subset of younger patients presenting with STEMI and assesses the frailty status of participants before the onset of acute illness. In our opinion, assessing frailty after the acute insult to the myocardium is likely to introduce bias in the evaluation.

4.1. Strengths and limitations

In our study, we have meticulously looked at the association between successful thrombolysis in elderly patients with ST-elevation myocardial infarction and a count of deficits, using a locally generated score relevant to the study population. This is the first study that uses a logistic regression model to explore this association to further develop ROC curves in order to identify patients who may be at a greater risk of a failed thrombosis. The present study is the first attempt to explore an association of accumulated health deficits with outcomes, especially in thrombolysed patients with ST-elevation myocardial infarction which is a reality for a larger proportion of patients in the developing world.

It is possible that the sickest patients who presented with myocardial infarction could not be thrombolysed successfully and hence were not captured in the study. In addition, our study also does not capture patients who died following a myocardial infarction but before reaching the hospital. This may introduce an element of bias against the sickest patients. Further, the premorbid frailty count of deficits was computed after they already had the episode of myocardial infarction and the element of recall bias cannot be completely eliminated. While a planned longitudinal study may be better suited to address the association, we feel that since all patients had an infarction, the bias would be similar across frail and non-frail individuals.

5. Conclusions

Our study indicates that frailty determined by a premorbid count of health deficits is associated with the outcome of thrombolysis following myocardial infarction in older patients. The patients with greater count of deficits have a higher chance of failure. Our findings will help informed decision-making while managing older patients presenting with myocardial infarction and in-turn improve morbidity and mortality.

Compliance with ethical standards

Acknowledgement

We acknowledge help of our CCU staff in collection of data

Disclosure of conflict of interest

No conflict of interest to disclosed.

Statement of ethical approval

The study for given approval by the Institutional Ethics Committee for Human Research at our college

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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