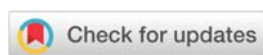


ORIGINAL ARTICLE

Clinical Frailty–Inflammation Phenotypes and Their Association with Treatment Failure in Older Medical Inpatients

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ABSTRACT

Background: Frailty and systemic inflammation could have a combined effect on recovery from acute illness in older people but their combined prognostic significance in general medical inpatients has not been fully characterized.

Objective: To determine the association between admission frailty–inflammation phenotypes and treatment failure among older medical inpatients.

Methods: This was a prospective observational cohort study of 100 patients ≥65 years of age during a 12-month period (January 2024 to January 2025) who were admitted to general medical wards at Sheikh Zayed Hospital Rahim Yar Khan. Frailty was determined by Clinical Frailty Scale (CFS); scores of 5–8 indicate frailty. Patients were divided into 4 groups: Robust–Low inflammation, Robust–High inflammation, Frail–Low inflammation, and Frail–High inflammation, according to the inflammation category. Treatment failure was defined as lack of clinical stability at day 5, escalation of major treatment, transfer to intensive care, or death in the hospital.

Results: There were 47 male and 53 female patients with the mean age 75.6 ± 7.5 years. 30 patients had treatment failure. Rates were 10.7%, 25.0%, 27.8%, and 50.0% across the four phenotypes, respectively ($p=0.008$). The frail–high inflammation phenotype was still associated with treatment failure (adjusted OR 5.72, 95% CI, 1.31–25.03; $p=0.020$) after adjustment. This group was also the group with the longest hospital stay, and the greatest incidence of functional decline.

Conclusions: Frailty and high inflammation were found to be most important in predicting treatment failure in older patients admitted to hospital. Clinical Frailty Scale and C-reactive protein provide a combined assessment which might be useful in the early risk stratification and individual inpatient management and to allow earlier multidisciplinary interventions during acute hospitalisation.

Keywords: clinical frailty; systemic inflammation; C-reactive protein; treatment failure; older inpatients; functional decline

INTRODUCTION

The increasing number of older adults admitted to medical wards has created substantial challenges for clinical assessment, treatment selection, and discharge planning¹. Older inpatients often have multimorbidity, polypharmacy,

impaired mobility, cognitive dysfunction and dependency in activities of daily living, and malnutrition. This cannot be accurately captured by chronological age, as there is great variation in physiological reserve and functional independence among people with the same chronological age².

Frailty is a multi-faceted clinical state of decreased physiological reserve and decreased resistance to acute stressors to health³. It is a progressive deterioration of musculoskeletal, neurological, metabolic, cardiovascular and immune systems. Thus, an apparently mild infection, a metabolic upset or aggravation of a chronic condition can lead to chronic instability, functional decline, institutionalization, or death in a frail person⁴.

There has been a growing use of the Clinical Frailty Scale in acute medical settings for its speed and convenience in assessing a person's health status prior to the onset of the current illness⁵. Mobility, cognition, comorbidity, functional independence, and need for assistance with activities of daily living are factors in the scale. In older inpatients, higher Clinical Frailty Scale scores have been linked to longer hospital stays, admission to intensive care, negative discharge outcomes, early readmission, functional loss, and higher death rates⁶.

Another important biological factor of vulnerability in later life is systemic inflammation⁷. As people get older, they experience a disturbance in immune function and ongoing low-grade inflammation (known as inflammaging). This underlying vulnerability can be exacerbated by the increased inflammatory response in the acute illness, increasing the risk of organ dysfunction, delayed recovery and poor clinical outcomes⁸.

C-reactive protein is a conveniently measurable measure of systemic inflammation and is commonly ordered when someone comes into the hospital for an acute admission⁹. Increased C-reactive protein levels can indicate infection, injury to tissues, acute organ dysfunction or exacerbation of chronic inflammatory conditions. In hospitalized older adults, higher concentrations of inflammatory-markers have been associated with death, longer hospital stay, treatment escalation and poor functional recovery¹⁰.

Frailty and inflammation are related but different aspects of risk in patients¹¹. Frailty is a measure of the patient's ability to withstand the physiological insult, while inflammatory activity is a measure of the acute biological insult. Coexistence may thus mark patients with limited physiological reserve who are unable to compensate for an increased inflammatory load during acute illness¹².

Using one assessment of frailty or inflammation alone might miss out key differences between older people¹³. A patient with strong immune system and with high levels of inflammation can make the recovery with proper care and treatment, but a patient with weak immune system and mild inflammation can still be at risk for functional decline and extended hospital stays. Patients with both frailty and high inflammation might constitute a more vulnerable phenotype who may be more likely to have ongoing clinical

instability, escalation of treatment, referral to intensive care or death¹⁴.

Although there is an increasing understanding of the independent predictive value of frailty and inflammatory markers, there are relatively few studies that have investigated the additive clinical effects of frailty and inflammatory markers in general medical inpatients¹⁵. The possibility of different phenotypes: robust–low inflammation, robust–high inflammation, frail–low inflammation and frail–high inflammation may offer a simple and clinically interpretable way of early risk stratification. This classification can also help facilitate greater surveillance, prompt multidisciplinary interventions, personalized intervention targets, and optimized discharge planning¹⁶.

The current study sought to identify the relationship between admission frailty–inflammation phenotypes and treatment failure in medical inpatients aged 65 years and older¹⁷. Concurrent clinical frailty and systemic inflammation were hypothesized to be associated with the most frequent treatment failure. The secondary outcome was to evaluate differences in hospital mortality, intensive care unit (ICU) transfer, length of stay, functional decline, institutional discharge and 30-day readmission between the four phenotypes¹⁸.

MATERIALS AND METHODS

Study Design and Setting: The study was a prospective observational cohort study carried out in the Department of Medicine at a tertiary care teaching hospital from January 2024 to 2025. Older adults were studied in general medical wards of Sheikh Zayed Hospital Rahim Yar Khan and the frailty inflammation phenotypes associations with treatment failure in hospital were assessed.

Study Population: Patients 65 years of age or older with an acute medical illness who were anticipated to have a hospital stay of 24 hours or more were deemed eligible. Common admission diagnoses were community acquired pneumonia, urinary tract infection, acute exacerbation of chronic obstructive pulmonary disease, acute heart failure, acute kidney injury, metabolic disturbances, as well as other general medical conditions. Patients who were not admitted via the emergency department, had been admitted and treated in another hospital for more than 48 hours, had been receiving palliative or end of life care, had a terminal malignancy, were unable to be reliably assessed for frailty, and were re-admitted during the study period were excluded. Only the first hospital admission eligible for the program was used for patients with multiple hospitalizations.

Sample Size and Sampling Technique: The number of patients who participated in the study were 100 patients collected by consecutive non-probability sampling technique. The patients were screened and recruited on an ad hoc basis from all eligible patients admitted during the study period until the sample size was reached.

Frailty Assessment: The Clinical Frailty Scale was used to measure frailty on the first day of hospital stay. The assessment was of the patient's health and mobility, cognition and functional independence, and need for help, around two weeks before the acute illness. Clinical Frailty Scale (CFS) scores of 1-4 were considered to represent robust or nonfrail; and scores of 5-8 were considered frail. Data was collected from the patient as far as possible and cross checked with caregivers and available medical records.

Assessment of Inflammation: As part of the routine clinical assessment, venous blood samples were taken within 24 hours of admission. The primary measure of systemic inflammation was serum C-reactive protein. Patients whose C-reactive protein level was less than 20 mg/L were considered as low level and those whose C-reactive protein level was 20 mg/L or more were classified as high level. Other laboratory tests performed were complete blood count, serum albumin, creatinine, urea, serum electrolytes, liver function tests and other tests as indicated in the presenting illness.

Frailty-Inflammation Phenotypes: Based on the Clinical Frailty Scale score and admission C-reactive protein level, patients were divided into four mutually exclusive phenotypes. The robust-low inflammation phenotype consisted of patients with a Clinical Frailty Scale score of 1-4 and a C-reactive protein level of less than 20 mg/L. The robust-high inflammation phenotype was defined as those with a Clinical Frailty Scale (CFS) score of 1-4 and a C-reactive protein (CRP) level ≥ 20 mg/L. The frail-low inflammation phenotype was defined as Clinical Frailty Scale 5 to 8 and C-reactive protein < 20 mg/L and the frail-high inflammation phenotype as Clinical Frailty Scale 5 to 8 and C-reactive protein ≥ 20 mg/L.

Data Collection: Structured data collection form was used to collect demographic, clinical and laboratory data. Variables were: age, sex, smoking status, BMI, residence, admission diagnosis, duration of illness before admission, comorbidities, polypharmacy, dependence in activities of daily living, cognition impairment, and nutritional risk. The initial clinical evaluation included blood pressure, heart rate, respiratory rate, body temperature, oxygen saturation, level of consciousness, oxygen requirement and

organ dysfunction. Chronic disease burden was estimated using Charlson Comorbidity Index and polypharmacy was defined as the regular use of 5 or more medications.

Primary Outcome: The main endpoint was failure of treatment during the index hospitalization. Treatment failure was defined as not being clinically stable within 5 days of treatment, deterioration of the underlying medical condition, necessitating a major treatment change or increase, use of vasopressor support, initiation of invasive mechanical ventilation or renal replacement therapy, transfer to a high dependency or intensive care unit or in-hospital mortality. Clinical stability was defined as: stable haemodynamic status, improving respiratory function, stable mental status, no new organ dysfunction and documented improvement of the condition responsible for admission.

Secondary Outcomes: The secondary outcome measures were intensive care (ICU) transfer, in-hospital mortality, length of stay, worsening function at discharge, new institutional placement, and hospital readmission within 30 days. Functional decline was the occurrence of new dependence in one or more basic activities of daily living (ADL) compared with the patient's pre-morbid level of functioning. Hospital records or telephone follow-up post-discharge determined 30-day readmission.

Outcome Assessment: The patients were inspected every day from admission till discharge or death. Treatment response, organ dysfunction, escalation of therapy, intensive care transfer, clinical complications and final hospital outcomes were recorded. The functional status at discharge was compared to the patients' baseline functional independence. Classification of outcome was done by using the predetermined criteria and cases of doubt were reviewed by two physicians. Any disagreement was resolved through discussion and consensus.

Ethical Considerations: Before the patients were recruited, the study protocol was approved by the institutional research ethics committee. Each participant or parent / guardian gave informed consent for their participation. Confidentiality was ensured by using coded study numbers and no personally identifiable data was included in the analysis. The final manuscript should have the official ethical approval number and name of the approving institution inserted in the manuscript.

Statistical Analysis: IBM SPSS Statistics was used for data entry and analysis. Normally distributed continuous variables were expressed as mean $\pm$ standard deviation and non-normally distributed continuous variables were

expressed as median and interquartile range. Categorical data were presented as numbers and percentages. One-way analysis of variance or Kruskal–Wallis test was used to compare continuous variables, and chi-square test or Fisher's exact test was used for categorical variables, among the four frailty–inflammation phenotypes.

Univariable logistic regression analysis was used to determine factors associated with treatment failure. All variables of clinical importance and those with an association of $p < 0.20$ in the univariable analyses were selected for inclusion in a multivariable logistic regression model. Frailty–inflammation phenotype, age, sex, comorbidity burden, admission diagnosis, acute illness severity, serum albumin, renal function and nutritional risk were selected for the final model. Adjusted odds ratios and 95% confidence intervals are presented. The sensitivity and specificity of the models were evaluated by the area under the receiver operating characteristic curve and by a p value < 0.05 .

RESULTS

Participant Enrollment and Phenotype Distribution: From January 2024 to January 2025, a total of 112 older medical inpatients were screened for eligibility. Twelve patients, four of whom were admitted directly to intensive care, three of whom were under palliation or end of life care, three of whom had insufficient data for reliable frailty assessment and two were transferred after having been treated at another institution for more than 48 hours, were excluded. A total of 100 patients (47 male and 53 female) were in the final analysis.

Based on admission Clinical Frailty Scale scores and C-reactive protein concentrations, 28 patients were identified as being robust–low inflammation, 20 were robust–high inflammation, 18 were frail–low inflammation and 34 were frail–high inflammation. All four phenotypes were represented by both male and female patients.

Baseline Demographic and Clinical Characteristics: The mean age of the subjects was 75.6 ± 7.5 year. Among the 100 patients, 47% were male and 53% were female. A total of 14 males and 14 females were in the robust–low inflammation group, 10 in the robust–high group, eight in the frail–low group, and 15 in the frail–high group. The sex distribution was not significantly different between the four phenotypes as seen in the table 1.

The mean age and Clinical Frailty Scale score were significantly higher in the frail phenotypes than in the robust groups. Frail patients also had more dependant activities of daily living and more chronic diseases and were more likely to have polypharmacy. The frail–high inflammation group had the highest median Charlson

Comorbidity Index and the highest prevalence of impaired renal function and nutritional risk as shown in Table 1.

Admission C-reactive protein levels and N/L ratios were significantly higher in the high-inflammation phenotypes than in the low-inflammation phenotypes. Patients with low inflammation and frailty had the lowest levels of serum albumin. The robust–high and frail–high inflammation groups had a higher number of infectious admission diagnoses. Similarly, a quick Sequential Organ Failure Assessment score of 2 or more was also most common in the frail–high inflammation group, although the association was not significant as shown in Table 1.

Treatment Failure: Treatment failure occurred in 30 of the 100 patients, giving an overall event rate of 30.0%. It was gradually increasing from one of the 4 phenotypes to the other. Three patients in the robust–low inflammation group, five patients in the robust–high inflammation group, five patients in the frail–low inflammation group and 17 patients in the frail–high inflammation group had treatment failure. The difference between the phenotypes was statistically significant, as indicated in the table below (Table 2).

Of robust patients who had low inflammation, 10.7% had treatment failure while 25.0% of robust patients with high inflammation and 27.8% of frail patients with low inflammation had treatment failures. The mortality rate due to treatment failure was 50.0% in patients who were both frail and had high inflammation. Hence, the frail–high inflammation phenotype had the highest odds of insufficient therapeutic response to inpatient treatment as shown in Table 2.

In the group of 47 male patients, 15 (31.9% of all males) failed treatment. There were also 15 out of 53 female patients who failed treatment, accounting for 28.3% of all females. There were no significant differences in the number of treatment failures between males and females.

The most common single component of the primary outcome was failure to reach clinical stability within 5 days and this was present in 23 patients. Major treatment escalation was necessary in 17 patients, 11 patients required transfer to intensive care and six patients died in hospital. The frail–high inflammation phenotype was most common for each of the components. Intensive care transfer and in-hospital mortality were not different, however, due to the relatively small number of events, as reported in Table 2.

Secondary Clinical Outcomes: The length of hospital stay was significantly different between the 4 phenotypes. For the robust–low inflammation group, the median hospital stay was five days, for the robust–high inflammation group it was six days, for the frail–low inflammation group it was

seven days and for the frail–high inflammation group it was nine days. These findings revealed a linear association

between the level of frailty and inflammatory burden and length of stay in the hospital, as illustrated in Table 2.

Table 1: Baseline characteristics according to frailty–inflammation phenotype

Characteristic	Robust–low inflammation (n=28)	Robust–high inflammation (n=20)	Frail–low inflammation (n=18)	Frail–high inflammation (n=34)	p value
Age, years	71.5 ± 5.4	73.2 ± 6.1	78.1 ± 6.8	79.0 ± 7.2	<0.001
Male sex	14 (50.0)	10 (50.0)	8 (44.4)	15 (44.1)	0.954
Female sex	14 (50.0)	10 (50.0)	10 (55.6)	19 (55.9)	0.954
Clinical Frailty Scale score	3 (2–4)	3 (3–4)	6 (5–6)	6 (5–7)	<0.001
Charlson Comorbidity Index	3 (2–4)	4 (2–5)	5 (4–6)	6 (4–7)	<0.001
Polypharmacy	8 (28.6)	8 (40.0)	12 (66.7)	25 (73.5)	0.002
Baseline dependence in activities of daily living	3 (10.7)	3 (15.0)	8 (44.4)	20 (58.8)	<0.001
Quick Sequential Organ Failure Assessment score ≥2	1 (3.6)	3 (15.0)	3 (16.7)	9 (26.5)	0.111
Infectious admission diagnosis	8 (28.6)	12 (60.0)	6 (33.3)	22 (64.7)	0.013
C-reactive protein, mg/L	7.4 (4.1–12.0)	61.5 (34.0–105.8)	8.2 (4.7–13.5)	74.0 (42.2–128.5)	<0.001
Serum albumin, g/dL	3.8 ± 0.4	3.4 ± 0.5	3.4 ± 0.5	3.0 ± 0.6	<0.001
Neutrophil-to-lymphocyte ratio	3.1 (2.2–4.5)	6.8 (4.6–10.4)	3.7 (2.5–5.4)	8.6 (5.7–13.4)	<0.001
Estimated glomerular filtration rate <45 mL/min/1.73 m ²	3 (10.7)	4 (20.0)	7 (38.9)	15 (44.1)	0.019
Nutritional risk	3 (10.7)	4 (20.0)	8 (44.4)	19 (55.9)	0.001

Table 2: Primary and secondary outcomes according to frailty–inflammation phenotype

Outcome	Robust–low inflammation (n=28)	Robust–high inflammation (n=20)	Frail–low inflammation (n=18)	Frail–high inflammation (n=34)	p value
Treatment failure	3 (10.7)	5 (25.0)	5 (27.8)	17 (50.0)	0.008
Failure to achieve clinical stability by day 5	2 (7.1)	4 (20.0)	4 (22.2)	13 (38.2)	0.036
Major treatment escalation	1 (3.6)	3 (15.0)	3 (16.7)	10 (29.4)	0.062
Intensive care transfer	1 (3.6)	2 (10.0)	2 (11.1)	6 (17.6)	0.372
In-hospital mortality	0 (0.0)	1 (5.0)	1 (5.6)	4 (11.8)	0.280
Length of hospital stay, days	5 (4–6)	6 (4–8)	7 (5–9)	9 (6–13)	<0.001
Functional decline at discharge	3 (10.7)	4 (20.0)	6 (33.3)	14 (41.2)	0.044
New institutional placement	1 (3.6)	1 (5.0)	3 (16.7)	7 (20.6)	0.135
Thirty-day unplanned readmission among discharged patients	2 (7.1)	3 (15.8)	3 (17.6)	9 (30.0)	0.157

Table 3: Logistic regression analysis of factors associated with treatment failure

Variable	Unadjusted odds ratio (95% confidence interval)	p value	Adjusted odds ratio (95% confidence interval)	p value
Robust–low inflammation	Reference	—	Reference	—
Robust–high inflammation	2.78 (0.58–13.34)	0.201	2.18 (0.42–11.34)	0.355
Frail–low inflammation	3.21 (0.66–15.59)	0.148	2.46 (0.47–12.91)	0.286
Frail–high inflammation	8.33 (2.08–33.41)	0.003	5.72 (1.31–25.03)	0.020
Female sex compared with male sex	0.84 (0.35–2.02)	0.701	—	—
Charlson Comorbidity Index ≥5	2.58 (1.08–6.15)	0.033	1.64 (0.66–4.10)	0.289
Quick Sequential Organ Failure Assessment score ≥2	4.12 (1.41–12.01)	0.009	3.09 (1.11–8.62)	0.031
Serum albumin <3.0 g/dL	3.36 (1.36–8.31)	0.009	2.57 (1.01–6.54)	0.048
Estimated glomerular filtration rate <45 mL/min/1.73 m ²	2.21 (0.91–5.39)	0.080	—	—
Nutritional risk	2.47 (1.02–5.97)	0.045	—	—

At discharge, 27 patients experienced a functional decline, which was significantly higher in both frail phenotypes. 10.7% in the robust–low inflammation group, 20.0% in the robust–high inflammation group, 33.3% in the frail–low inflammation group, and 41.2% in the frail–high inflammation group. Twelve patients required new institutional placement, with the tendency being highest for the frail patients with high inflammation, although this was not statistically significant, as explained in Table 2.

Among the 94 patients who left the hospital alive, 17 were readmitted within 30 days. Patients with robust–low inflammation group had readmission in two, robust–high inflammation group, three; frail–low inflammation group, three; and frail–high inflammation group, nine. The frequency was highest in the frail–high inflammation phenotype, but the difference was not statistically significant as shown in Table 2.

Association Between Sex and Treatment Failure: Treatment failure affected 15 of 47 male patients and 15 of 53 female patients. There was no difference between female and male sex in relation to treatment failure. Table 3 shows that the odds ratio for female sex was 0.84 (95% CI 0.35–2.02) with a p value of 0.701. These results suggested that the relationship between frailty–inflammation phenotype and treatment failure was not due to sex imbalance or sex-specific effects.

Factors associated with treatment failure: In the univariable model, patients with the robust–high inflammation phenotype were 2.78 times more likely to experience treatment failure than patients with the robust–low inflammation phenotype. For the frail–low inflammation group, the odds were three times higher and, for the frail–high inflammation group, the odds were eight times higher. The association was statistically significant for the frail–high inflammation phenotype as shown in Table 3.

Charlson Comorbidity Index ≥ 5 , rapid Sequential Organ Failure Assessment score ≥ 2 , serum albumin < 3.0 g/dL and impairment in renal function were also assessed as potential predictors. Due to the small number of treatment failure events ($n = 30$), a parsimonious multivariable model was developed to avoid overfitting the model. Frailty–inflammation phenotype, comorbidity burden, acute physiological severity and hypoalbuminemia were selected as the final model.

The frail–high inflammation phenotype continued to be independently associated with failure to treatment after adjustment. In this category, patients had 5.72 times higher odds of treatment failure when compared with robust patients with low inflammation after adjustment. Other variables independently associated with the primary

outcome were a rapid SOFA score of 2 or more and serum albumin of less than 3.0 g/dL (Table 3).

Model Performance: The area under the receiver operating characteristic curve for the regression model including only the frailty–inflammation phenotype was 0.70. When the comorbidity burden, quick Sequential Organ Failure Assessment score, and serum albumin were added to the model, it achieved an acceptable discrimination of treatment failure, with an area under the curve of 0.79. The Hosmer–Lemeshow goodness-of-fit test resulted in a p value of 0.614, which showed adequate calibration of the model. The assessment of frailty and inflammatory status combined thus offered clinically useful prognostic information over and above either factor alone.

DISCUSSION

The current study showed that a dual evaluation of both frailty and systemic inflammation was meaningful in the prognosis of older medical inpatients¹⁹. A total of 30% experienced treatment failure, which was higher with each clinical phenotype. Patients with high inflammation who were classified as being frail had the worst outcomes, with one-half experiencing a treatment failure, as opposed to 10.7% of those who are robust with low inflammation. This pattern indicates that the degree of inflammatory response and baseline physiological vulnerability combine to impact recovery from acute medical illness²⁰.

Frailty is a decreased capacity to cope with stress³. Patients aged 65 years and older who are at risk of frailty often suffer from mobility problems, sarcopenia, poor nutrition, cognitive vulnerability, multimorbidity, and dependence in everyday activities. These factors may reduce their ability to withstand infection, acute organ failure, metabolic derangements, or cardiovascular decompensation. In the current study, frail patients were older, had higher comorbidity, a higher incidence of polypharmacy, less functional independence, and higher nutritional risk compared to robust patients. Such properties probably helped explain their poor response to conventional inpatient treatment⁷.

Another important determinant of clinical deterioration is systemic inflammation⁸. High-inflammation phenotypes were significantly associated with increased C-reactive protein and neutrophil-to-lymphocyte ratio, and decreased serum albumin. These results suggest a higher acute inflammatory and catabolic load. Excessive inflammation could play a role in endothelial dysfunction, immune function, muscle breakdown, decreased appetite, poor tissue healing, and organ function. These can delay clinical stabilisation and the need for escalation of therapy¹².

High frailty and high inflammation had the highest association with treatment failure⁵. The frail-high inflammation phenotype was independently associated with treatment failure in multivariable analysis, even when adjusting for a co-morbidity burden, acute physiological severity and hypoalbuminemia. Patients in this group were over five times as likely to experience treatment failure as robust patients with low inflammation, after taking other factors into account. However, isolated frailty or isolated high inflammation was not itself significant when adjusted for. This discovery suggests that twin phenotype could provide more clinically relevant information than either phenotype alone¹⁴.

One explanation is that inflammation is a measure of the severity of the acute physiological insult and frailty a measure of a patient's ability to withstand the insult⁶. In a healthy patient, there may be a significant inflammatory reaction, but enough physiological reserve remains for the patient to recover. Likewise, a debilitated patient with a low inflammatory load might benefit from therapy even with a relatively mild acute episode. However, if severe inflammation is 'grafted' onto frailty, the patient may not be able to recover normal function, leading to ongoing instability, escalation of care, transfer to intensive care or death¹⁷.

Frailty-high inflammation was also linked to a longer hospital stay⁹. Median hospital stay was 5 days for those who were robust with low inflammation and 9 days for those who were frail with high inflammation. Extended hospitalizations could be indicative of prolonged recovery from the acute illness, increased complexity of care, a delay in mobilization, greater functional decline and more complex discharge planning. Older patients may be at risk for more complications during longer hospitalizations, including delirium, hospital acquired infection, falls, development of pressure injuries and deconditioning¹³.

Another important finding was that of functional decline at discharge⁴. Over 40% of the patients who were both frail and had high inflammation had new ADL dependence. This finding highlights the importance of assessing successful therapy in older people not only in terms of survival or improvement of laboratory parameters. The patient may recover from this acute illness, but be discharged from the hospital with significantly decreased mobility and independence. Thus, early physiotherapy, nutritional support, delirium prevention, medication review and mobilization may be more relevant for patients with characteristics of frailty at admission and high levels of inflammation¹⁶.

The frail-high inflammation group had the highest number of 30-day readmissions¹⁰. The difference was not significant but almost a third of surviving patients in this phenotype were readmitted. Factors that could lead to

early return to hospital include persistent inflammation, functional recovery, multimorbidity, medication complexity, and limited social support. This lack of statistical significance might have been due to the small number of patients and readmissions and not a lack of clinical association¹⁸.

Patients were well-balanced with regard to gender throughout the cohort and treatment failure rates were similar for both males and females². In regression analysis, female sex was not a factor associated with treatment failure. This finding implies that the observed relationship between phenotype and outcome was not due to sex imbalance. However, larger studies are required to explore if there is a biological interplay between frailty, inflammatory activity and recovery that is modified by sex¹¹.

Also, a rapid Sequential Organ Failure Assessment score ≥ 2 and serum albumin < 3.0 g/dL proved to be independent risk factors for treatment failure¹⁵. Association with acute physiological severity was anticipated, as patients with more organ dysfunction will be less likely to stabilise quickly. Hypoalbuminemia may be due to inflammation, malnutrition, chronic disease or increased catabolic activity. The independent association supports the significance of examining both inflammatory and nutritional status in older hospitalized patients⁸.

Assessment of frailty-inflammation phenotype, comorbidity burden, acute severity and serum albumin as a group led to improvement in the predictive performance of the model¹. This suggests that a multi-dimensional strategy might be more valuable than the use of only one biomarker or clinical score. The Clinical Frailty Scale is easily accessible and widely used in routine care, as is C-reactive protein, and the proposed phenotype classification is simple, inexpensive, and potentially may be used for early risk assessment in the wards¹⁹.

The frail-high inflammation phenotype identified at admission could be used to guide more frequent monitoring and the provision of earlier multidisciplinary care⁷. These patients could benefit from senior clinical review, prompt enquiry into reversible causes, optimising antimicrobial and/or disease-specific treatment, early nutritional assessment, physiotherapy, delirium prevention and structured discharge planning. However, the frailty classification should not be used to limit appropriate care just because a patient is frail. Rather, it might help a clinician identify vulnerability, plan for potential complications, have conversations about realistic treatment goals and individualize care¹³.

There are some caveats to note. The sample size in the study was relatively small and from a single centre, and may not be generalizable⁶. The level of C-reactive protein is a non-specific biomarker and can vary depending on diagnosis, timing of blood sample, chronic inflammatory

diseases, malignancy, obesity, and the use of certain medications. One admission measurement may not be representative of the inflammatory process that follows. Re-iterative measurements might yield further prognosis data¹⁰.

A composite outcome of treatment failure was used, which included several clinically distinct events⁴. This made the number of outcome events higher, but might not be of equal clinical importance. Clinician judgement, resource availability, patient preferences, and limitations of care may also play a role in treatment escalation and/or intensive care transfer. The number of events limited the number of variables that can be safely added to the multivariable model and residual confounding cannot be ruled out¹⁵.

This study introduces a clinically relevant framework for the integration of baseline vulnerability with acute inflammatory burden, despite its limitations¹². The proposed phenotypes should be confirmed by larger, multicentre studies, which would also help identify the best inflammatory thresholds. Future investigations should also be conducted to assess serial changes in C-reactive protein, to compare other inflammatory markers, and to investigate whether there is any benefit of targeted multidisciplinary interventions to decrease rate of failure in high-risk patients²⁰.

CONCLUSION

Older medical inpatients who were clinically frail and had high systemic inflammation were at the highest risk for treatment failure. Frailty–high inflammation phenotype was independently linked to insufficient treatment response, length of hospital stay, functional decline and increased early readmission rates. Frailty and inflammation seemed to add additional information, and both measures together resulted in a higher prediction level than either measure alone. Use of the Clinical Frailty Scale and C-reactive protein on admission could help to stratify risk and provide more individualised inpatient care. Prospective, multicentre studies are needed with larger patient numbers to validate these results and determine if phenotype-guided interventions correlate with better clinical and functional outcomes.

DECLARATION

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