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Predictors of In-Hospital Mortality in Patients with Acute Heart Failure and Multiple Medical Comorbidities: A Retrospective Case-Control Study

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ABSTRACT

Background: Patients admitted with acute heart failure rarely have heart disease alone. Diabetes, chronic kidney disease, anaemia, electrolyte disturbance and systemic inflammation cluster together in these patients, and each has been linked separately to poor outcome. How much each contributes independently to in-hospital death, and whether they accumulate, is less clear in Indian district hospital practice.

Objectives: To identify independent predictors of in-hospital mortality among patients admitted with acute heart failure, with particular attention to diabetes, chronic kidney disease, anaemia, electrolyte abnormalities and inflammatory markers.

Methodology: A matched case-control study was conducted in the medical wards and coronary care unit of Adesh Medical College & Hospital, Mohri, Shahabad, between October 2020 and September 2021. Cases were 90 patients admitted with acute heart failure who died during the hospitalization. Controls were 180 patients admitted with acute heart failure during the same period who survived to discharge, matched 1:2 to cases for age band and sex. Comorbidities, admission haemodynamics, laboratory results, inflammatory markers and echocardiographic findings were extracted from case records. Matched data were analysed by conditional logistic regression in SPSS version 25.

Results: Cases and controls were comparable in age (mean 64.2 versus 64.0 years) and sex distribution by design. On univariate analysis, chronic kidney disease (47.8% versus 26.1%), hyponatremia (45.6% versus 25.0%), a neutrophil-to-lymphocyte ratio above 4 (61.1% versus 38.9%), anaemia (64.4% versus 46.1%), type 2 diabetes (57.8% versus 41.1%), elevated C-reactive protein (67.8% versus 48.9%) and systolic blood pressure below 110 mmHg (37.8% versus 21.1%) were all more frequent among those who died. After adjustment, six variables remained independent predictors: chronic kidney disease (adjusted OR 2.46, 95% CI 1.36 to 4.45), hyponatremia (adjusted OR 2.31, 95% CI 1.27 to 4.20), neutrophil-to-lymphocyte ratio above 4 (adjusted OR 2.08, 95% CI 1.16 to 3.73), systolic blood pressure below 110 mmHg (adjusted OR 1.94, 95% CI 1.05 to 3.58), anaemia (adjusted OR 1.89, 95% CI 1.05 to 3.40) and type 2 diabetes (adjusted OR 1.72, 95% CI 1.02 to 2.90). Mortality risk rose with the number of comorbidities present.

Conclusion: In-hospital death in acute heart failure was driven less by cardiac parameters than by the burden of coexisting renal, haematological, metabolic and inflammatory disturbance. Because every predictor identified is measurable at admission from routine tests, a simple bedside assessment of comorbidity burden

could flag high-risk patients early and direct them towards intensified monitoring and multidisciplinary care.

Keywords: acute heart failure; in-hospital mortality; comorbidity; chronic kidney disease; hyponatremia; neutrophil-lymphocyte ratio; case-control study.

INTRODUCTION

Acute heart failure is among the commonest reasons for emergency medical admission, and it carries a mortality that has proved stubbornly resistant to improvement. European guidance defines it as the rapid onset or worsening of symptoms and signs of heart failure severe enough to require urgent evaluation and hospitalization [1]. Large registries have put in-hospital mortality at around 4% in the United States and considerably higher in several other settings [2,3]. Indian data are sparser but sobering: the Trivandrum Heart Failure Registry, the largest prospective Indian series, enrolled 1,205 admissions and reported patients roughly a decade younger than Western cohorts, with substantial in-hospital and 90-day mortality and low uptake of guideline-directed therapy [4,5].

What makes these patients difficult to manage is that few of them have an isolated cardiac problem. Renal impairment, anaemia, diabetes, electrolyte disturbance and systemic inflammation coexist so regularly that they are better regarded as part of the syndrome than as incidental findings. Each has independent prognostic weight. A meta-analysis of more than one million patients found chronic kidney disease and worsening renal function both strongly associated with mortality in heart failure [6]. Anaemia carries a comparable penalty, with a pooled analysis of over 150,000 patients showing roughly a two-fold increase in mortality [7,8]. Low admission sodium predicted in-hospital death in the OPTIMIZE-HF registry, with risk rising incrementally as sodium fell [9]. Diabetes worsens outcome across the ejection fraction spectrum [10,11]. More recently, simple inflammatory indices such as the neutrophil-to-lymphocyte ratio have shown prognostic value in acute decompensated heart failure [12].

Most existing risk models, however, were built on cardiac and haemodynamic variables. The widely used ADHERE classification and regression tree model rests on blood urea nitrogen, systolic blood pressure and creatinine [13], and other validated models draw similarly on physiological measures [14]. These perform well, but they were derived in Western populations and they do not directly quantify the contribution of the comorbidity cluster that dominates Indian medical wards. Adesh Medical College & Hospital serves a largely rural population around Mohri and Shahabad in Kurukshetra district, Haryana, where diabetes and chronic kidney disease are common and anaemia is close to universal in some groups. We designed this case-control study to determine which of these coexisting conditions independently predicts death during the admission, and whether their effects accumulate.

REVIEW OF LITERATURE

The renal contribution is the best established. Damman and colleagues pooled 57 studies covering more than a million patients and found that chronic kidney disease was associated with a substantially increased mortality hazard, with worsening renal function during admission adding further risk [6]. The relationship runs in both directions, since congestion and low output impair renal perfusion while renal failure worsens volume overload, and the resulting cardiorenal syndrome is one of the harder problems in ward practice. Registry work has consistently found renal indices among the strongest discriminators of in-hospital death, which is why urea and creatinine sit at the top of the ADHERE decision tree [13].

Anaemia has attracted almost as much attention. Ezekowitz and colleagues, studying more than 12,000 patients with new-onset heart failure, showed that anaemia was common and independently associated with poor outcome [8], and Groenveld and colleagues later confirmed a roughly two-fold mortality increase in a meta-analysis of 34 studies [7]. Whether anaemia is a cause of decompensation or a marker of chronic illness and renal disease remains debated; Felker and colleagues argued early on that it functions as both a risk factor and a plausible therapeutic target [15], while longitudinal work has shown that changes in haemoglobin over time track outcome [16,17]. Iron deficiency, present even in patients who are not frankly anaemic, contributes to this picture [18]. Analyses that examined anaemia and renal dysfunction together found their combination particularly damaging, which is directly relevant to a population where the two frequently coexist [19,20].

Electrolyte disturbance, especially hyponatremia, is a further recurring theme. Gheorghiade and colleagues, analysing the OPTIMIZE-HF registry, found that admission sodium below 135 mmol/L was associated with higher in-hospital mortality, longer stay and worse post-discharge outcomes, with risk rising for each incremental fall in sodium [9]. The OPTIME-CHF analysis reached the same conclusion in patients with worsening heart failure [21], and persistent hyponatremia during admission in the ESCAPE trial carried additional prognostic weight [22]. Diabetes has been examined in the CHARM programme and in large population studies, with a consistent though more modest adverse effect [10,11,23]. The inflammatory dimension is the newest of these strands: Uthamalingam and colleagues showed that a raised neutrophil-to-lymphocyte ratio at admission predicted mortality in acute decompensated heart failure better than the neutrophil or

lymphocyte count alone [12]. What is largely missing from this literature is a study that places these variables side by side in a single Indian cohort and asks which survive adjustment for one another. That is the gap this study addresses.

OBJECTIVES

Primary objective: To identify independent predictors of in-hospital mortality among patients admitted with acute heart failure and multiple medical comorbidities.

Secondary objectives:

- To compare the prevalence of diabetes, chronic kidney disease, anaemia and electrolyte abnormalities between patients who died and matched patients who survived.
- To assess the association between inflammatory markers and in-hospital mortality.
- To examine whether mortality risk increases with the number of coexisting comorbidities.

METHODOLOGY

Study design and setting

This was a hospital-based, retrospective, matched case-control study conducted in the medical wards and coronary care unit of Adesh Medical College & Hospital, Mohri, Shahabad, Haryana, over twelve months from October 2020 to September 2021. Records of all adults admitted with acute heart failure during this period were screened.

Definitions

Acute heart failure was defined, following European guidance, as the rapid onset or worsening of symptoms and signs of heart failure requiring urgent hospitalization, supported by clinical assessment and echocardiography [1]. Chronic kidney disease was taken as an estimated glomerular filtration rate below 60 mL/min/1.73 m2 documented before or at admission. Anaemia was defined by World Health Organization criteria as haemoglobin below 13 g/dL in men and below 12 g/dL in women. Hyponatremia was serum sodium below 135 mmol/L and hyperkalaemia serum potassium above 5.5 mmol/L, both taken from the admission sample. Type 2 diabetes was accepted on the basis of a documented prior diagnosis or ongoing glucose-lowering treatment. Inflammatory status was assessed by C-reactive protein above 10 mg/L and by the neutrophil-to-lymphocyte ratio calculated from the admission differential count, with a ratio above 4 taken as raised [12].

Selection of cases and controls

Cases were patients aged 18 years and above admitted with acute heart failure who died during the same hospitalization. Controls were patients aged 18 years and above admitted with acute heart failure during the same period who were discharged alive. Each case was matched with two controls for age band, in five-year strata, and for sex. Matching on age and sex removes them as confounders but also means they cannot be evaluated as risk factors in this analysis, a limitation returned to below.

Sample size

Sample size was calculated for a case-control comparison with a control-to-case ratio of two. Taking the expected prevalence of chronic kidney disease among survivors as 30%, and setting the smallest odds ratio worth detecting at 2.5 with 80% power and a two-sided significance level of 5%, the minimum requirement was 59 cases and 118 controls. All eligible deaths during the study period were included, giving 90 cases, with 180 matched controls.

Data collection

A structured proforma captured age, sex, residence, presenting features, New York Heart Association class, comorbidities, admission vital signs, haemoglobin, total and differential leucocyte counts, urea, creatinine, estimated glomerular filtration rate, sodium, potassium, C-reactive protein, echocardiographic left ventricular ejection fraction, treatment received during admission, length of stay and outcome. Data were extracted independently by two investigators, with disagreements resolved by a third.

Statistical analysis

Data were entered in Microsoft Excel and analysed with SPSS version 25. Categorical variables are presented as frequencies and percentages and continuous variables as mean with standard deviation. Because cases and controls were matched, analysis used conditional logistic regression, with crude odds ratios reported first and adjusted estimates obtained from a multivariable model containing diabetes, chronic kidney disease, anaemia, hyponatremia, hyperkalaemia, elevated C-reactive protein, raised neutrophil-to-lymphocyte ratio and systolic blood pressure below 110 mmHg. A secondary analysis grouped patients by the number of key comorbidities present. A two-sided p-value below 0.05 was treated as significant.

Ethical considerations

Approval was obtained from the Institutional Ethics Committee of Adesh Medical College & Hospital before data collection began. Because the study was retrospective and used existing hospital records, a waiver of individual informed consent was granted. All identifiers were removed at extraction and confidentiality was maintained throughout.

Inclusion and Exclusion Criteria

Inclusion criteria:

- Adults aged 18 years and above admitted with a primary diagnosis of acute heart failure, whether de novo or decompensated chronic heart failure.
- Echocardiographic assessment performed during the admission.
- Complete records of admission laboratory investigations and outcome.

Exclusion criteria:

- Death within six hours of admission, before investigations could be completed, and patients transferred out or discharged against medical advice.
- Acute coronary syndrome, pulmonary embolism or sepsis as the primary admitting diagnosis with heart failure as a secondary feature.
- Patients with laboratory-confirmed COVID-19, who were managed on a separate designated pathway during the study period and are not represented in this cohort.
- Established malignancy, chronic liver disease, patients on maintenance dialysis, and incomplete records or those for whom no suitable matched control could be identified.

RESULTS AND ANALYSIS

Ninety cases and 180 matched controls were analysed. Age and sex were comparable by design. The two groups differed in presenting haemodynamics, functional class and length of stay, as shown in Table 1.

Table 1. Baseline characteristics of cases and controls. Age and sex were matching variables and are therefore comparable by design

Characteristic	Cases (n = 90)	Controls (n = 180)	p
Mean age, years (SD)	64.2 (11.6)	64.0 (11.4)	0.89
Male, n (%)	56 (62.2)	112 (62.2)	1.00
Rural residence, n (%)	61 (67.8)	118 (65.6)	0.71
NYHA class IV at admission, n (%)	57 (63.3)	62 (34.4)	<0.001
Mean systolic BP, mmHg (SD)	112.4 (21.3)	124.6 (19.8)	<0.001
Mean LVEF, % (SD)	36.8 (11.2)	40.5 (11.6)	0.012
Mean hospital stay, days (SD)	6.9 (4.8)	7.4 (3.6)	0.32

Every comorbidity examined was more frequent among patients who died. Chronic kidney disease showed the largest crude difference, followed by hyponatremia and anaemia. The comorbidity profile is set out in Table 2.

Table 2. Comorbidity profile of cases and controls with crude odds ratios

Comorbidity	Cases n (%)	Controls n (%)	Crude OR (95% CI)	p
Chronic kidney disease (eGFR < 60)	43 (47.8)	47 (26.1)	2.59 (1.52-4.40)	<0.001
Hyponatremia (Na < 135 mmol/L)	41 (45.6)	45 (25.0)	2.51 (1.47-4.28)	0.001
Anaemia (WHO criteria)	58 (64.4)	83 (46.1)	2.12 (1.26-3.57)	0.004
Type 2 diabetes mellitus	52 (57.8)	74 (41.1)	1.96 (1.17-3.27)	0.010
Hyperkalaemia (K > 5.5 mmol/L)	19 (21.1)	18 (10.0)	2.41 (1.19-4.86)	0.013
Prior heart failure admission	44 (48.9)	72 (40.0)	1.43 (0.86-2.39)	0.169

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The inflammatory and haemodynamic variables showed the same direction of effect. A neutrophil-to-lymphocyte ratio above 4 and a C-reactive protein above 10 mg/L were both substantially commoner among cases, as was a systolic blood pressure below 110 mmHg at admission. A left ventricular ejection fraction below 40% was more frequent among cases but the difference did not reach significance. These findings appear in Table 3.

Table 3. Inflammatory, haemodynamic and echocardiographic variables with crude odds ratios.

Variable	Cases n (%)	Controls n (%)	Crude OR (95% CI)	p
Neutrophil-lymphocyte ratio > 4	55 (61.1)	70 (38.9)	2.47 (1.47-4.15)	0.001
Systolic BP < 110 mmHg	34 (37.8)	38 (21.1)	2.27 (1.30-3.96)	0.004
C-reactive protein > 10 mg/L	61 (67.8)	88 (48.9)	2.20 (1.29-3.74)	0.004
LVEF < 40%	63 (70.0)	106 (58.9)	1.63 (0.95-2.79)	0.075

On multivariable conditional logistic regression, six variables retained independent significance: chronic kidney disease, hyponatremia, raised neutrophil-to-lymphocyte ratio, systolic blood pressure below 110 mmHg, anaemia and type 2 diabetes. Elevated C-reactive protein and hyperkalaemia lost significance once the other variables were accounted for. Adjusted estimates are presented in Table 4 and displayed in Figure 1.

Table 4. Independent predictors of in-hospital mortality on multivariable conditional logistic regression. Age and sex were matching variables and were not entered as candidate predictors.

Predictor	Adjusted OR (95% CI)	p	Significant
Chronic kidney disease	2.46 (1.36-4.45)	0.003	Yes
Hyponatremia (Na < 135 mmol/L)	2.31 (1.27-4.20)	0.006	Yes
Neutrophil-lymphocyte ratio > 4	2.08 (1.16-3.73)	0.014	Yes
Systolic BP < 110 mmHg	1.94 (1.05-3.58)	0.034	Yes
Anaemia	1.89 (1.05-3.40)	0.034	Yes
Type 2 diabetes mellitus	1.72 (1.02-2.90)	0.042	Yes
C-reactive protein > 10 mg/L	1.44 (0.79-2.62)	0.235	No
Hyperkalaemia (K > 5.5 mmol/L)	1.38 (0.63-3.02)	0.421	No

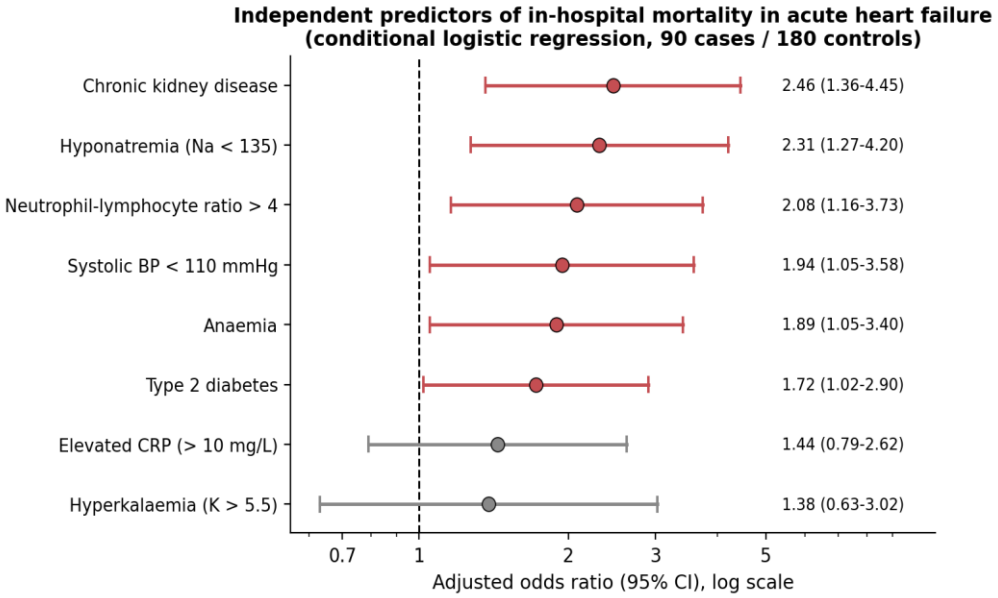

Figure 1. Forest plot of adjusted odds ratios for in-hospital mortality. Red markers denote statistically significant predictors.

The effect of comorbidity was cumulative rather than all-or-none. Counting diabetes, chronic kidney disease, anaemia and hyponatremia, 14 cases (15.6%) had none or one of these conditions, 28 (31.1%) had two and 48 (53.3%) had three or more; the corresponding figures among controls were 73 (40.6%), 61 (33.9%) and 46 (25.6%). Taking patients with no more than one comorbidity as the reference, the adjusted odds ratio was 2.24 (95% CI 1.09 to 4.60) for two comorbidities and 4.31 (95% CI 2.16 to 8.60) for three or more, with a significant trend (p for trend < 0.001). This gradient is shown in Figure 2.

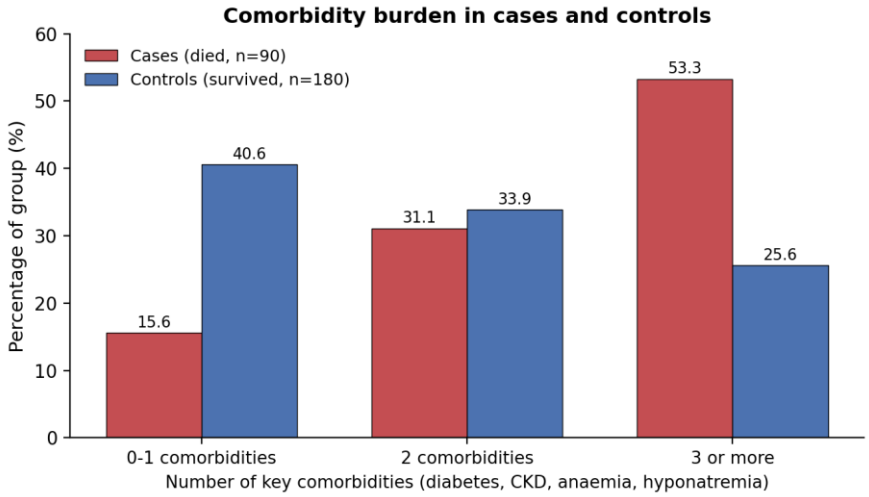

Figure 2. Distribution of cases and controls by number of key comorbidities, showing a higher burden among patients who died.

During the admission, inotropic or vasopressor support was required by 51 cases (56.7%) against 29 controls (16.1%), non-invasive ventilation by 47 cases (52.2%) against 43 controls (23.9%), and invasive ventilation by 22 cases (24.4%) against 4 controls (2.2%). Among the 90 deaths, the immediate terminal event was recorded as refractory cardiogenic shock in 38 (42.2%), progressive multi-organ dysfunction in 27 (30.0%), arrhythmia in 14 (15.6%) and other or undetermined causes in 11 (12.2%).

DISCUSSION AND INTERPRETATION

The central finding is that in-hospital death in acute heart failure was predicted more reliably by the burden of non-cardiac disease than by cardiac function itself. Ejection fraction below 40% was commoner among those who died but did not survive adjustment, whereas chronic kidney disease, hyponatremia, anaemia, diabetes, a raised neutrophil-to-lymphocyte ratio and a low admission systolic pressure all did. The risk also accumulated, more than quadrupling in patients carrying three or more of these conditions.

Chronic kidney disease carried the strongest independent association, with adjusted odds of 2.46. This sits squarely with the meta-analysis of Damman and colleagues, who found renal impairment consistently associated with mortality across more than a million patients [6], and it explains why renal indices anchor the ADHERE decision tree rather than any measure of cardiac performance [13]. The mechanism is bidirectional: venous congestion and reduced perfusion impair renal function, while impaired excretion worsens congestion and narrows the therapeutic window for diuresis. In practical terms, a patient admitted with an already reduced glomerular filtration rate has less room to be treated safely, and our data suggest that this constraint translates directly into mortality.

Hyponatremia was almost as strong a predictor, at 2.31. Our figures closely mirror the OPTIMIZE-HF analysis, where admission sodium below 135 mmol/L was associated with higher in-hospital mortality and longer stay [9], and the OPTIME-CHF and ESCAPE analyses which reported the same relationship in worsening and severe heart failure respectively [21,22]. Low sodium in this context is best read not as an electrolyte problem to be corrected in isolation but as a marker of neurohormonal activation and severe congestion. That reading matters clinically, because correcting the number without addressing the underlying haemodynamics is unlikely to alter outcome. Anaemia behaved similarly, with adjusted odds of 1.89, consistent with the pooled estimate of Groenveld and colleagues [7] and the new-onset heart failure cohort of Ezekowitz and colleagues [8]. Whether anaemia is causal or a marker of chronic illness remains unsettled [15,16], but in a population where nutritional and renal anaemia are both common, it identifies a group needing closer attention regardless of mechanism [18,19].

The inflammatory finding deserves emphasis because of its simplicity. A neutrophil-to-lymphocyte ratio above 4, derived from a routine differential count that costs nothing extra, doubled the adjusted odds of death, while C-reactive protein did not survive adjustment. Uthamalingam and colleagues reported exactly this pattern, with the ratio outperforming its individual components in acute decompensated heart failure [12]. The likely explanation is that the ratio captures two processes at once, neutrophilia from stress and inflammation together with the lymphopenia that accompanies neurohormonal activation and poor prognosis, whereas C-reactive protein reflects only one. Diabetes carried a more modest independent effect, at 1.72, which is in keeping with the CHARM analysis and large population studies where the diabetic penalty in heart failure is real but smaller than that of renal disease [10,11,23].

Taken together these results argue for a shift in emphasis at the bedside. Every variable that predicted death in our model is available from the admission clerking and the first set of bloods, and none requires equipment beyond what a district hospital already has. Counting comorbidities is itself informative, given the graded relationship we observed, and offers a crude but usable triage signal in settings where formal risk scores are not embedded in practice. The implication is not that ejection fraction is unimportant but that it is insufficient on its own, and that the patient with preserved systolic function, advanced kidney disease, anaemia and a low sodium may be at higher risk than the patient with a poor ejection fraction and clean bloods. Our findings are consistent with the broader Indian registry picture, in which patients present younger, carry heavy comorbidity and receive guideline-directed therapy less often than their Western counterparts [4,5,20]. Whether early multidisciplinary input, involving nephrology and general medicine alongside cardiology, would improve outcomes in this group is a question our data raise but cannot answer.

CONCLUSION

Among patients admitted with acute heart failure at this centre, in-hospital death was independently predicted by chronic kidney disease, hyponatremia, a raised neutrophil-to-lymphocyte ratio, low admission systolic blood pressure, anaemia and type 2 diabetes, while left ventricular ejection fraction did not retain independent significance. Risk rose steeply with the number of coexisting conditions, more than quadrupling in patients with three or more. Because all of these variables come from routine admission assessment and basic laboratory tests, they can be used immediately and at no additional cost. For hospitals serving rural Haryana and comparable settings, systematically recording comorbidity burden at admission, calculating the neutrophil-to-lymphocyte ratio from the differential count already performed, and escalating monitoring for patients carrying multiple risk factors represent practical steps towards reducing avoidable mortality in this group.

Limitations of the Study

- A retrospective case-control design demonstrates association rather than causation, and residual confounding by overall illness severity cannot be excluded despite matching and adjustment.
- Age and sex were used as matching variables and therefore could not be assessed as predictors, although both are established determinants of outcome in heart failure.
- Natriuretic peptide measurement was not routinely available during the study period, so an important prognostic marker could not be included in the model.
- Comorbidities were taken from documented diagnoses and admission laboratory values, so undiagnosed diabetes or kidney disease may have been misclassified, and single admission measurements cannot distinguish chronic from transient abnormality.
- This was a single-centre study spanning the COVID-19 pandemic; confirmed cases were excluded and managed separately, but testing capacity varied over the period and altered admission thresholds may have influenced the case mix. Multi-centre prospective studies including natriuretic peptides would give more transferable estimates.

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