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Outcomes and Utility of Troponin and NT-proBNP Testing in Dyspnoea Presentations

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Abstract

Aim

To describe the pattern and prognostic value of troponin (hscTnT) and NT-proBNP testing in dyspnoea presentations.

Methods

We studied all general medical admissions over 6 years (2015-2020). hscTnT and NT-proBNP were related to 30-day in-hospital mortality with a multivariable logistic regression model and to LOS and investigation count using zero truncated Poisson regression.

Results

Of 49,965 admissions, 7,087 (14.2%) were due to dyspnoea. Dyspnoea presentations were older, 69.6 vs. 64.8 years and had a longer length of stay (LOS) at 6.4 vs. 5.0 days. 30-day in-hospital mortality was higher, 7.4% vs 4.1% ($p<0.001$). Adjusting for illness severity and comorbidity attenuated the difference, 4.3% vs 4.1%. hscTnT and NT-proBNP were requested in 22.4% and 18.0% of admissions, respectively. hscTnT and NT-proBNP were requested in 39.5% and 41.8% of dyspnoea presentations respectively, with highest rates of 61.6% and 65.6% in cardiac cases. hscTnT, OR 1.24 (95%CI 1.16, 1.33), and NT-proBNP, OR 1.11 (95%CI 1.08, 1.15), were predictive of 30-day in-hospital mortality. The hospital LOS was dependent on total tests and procedures conducted; hscTnT and NT-proBNP testing had limited effect.

Conclusion

Dyspnoea presentations have worse outcomes. hscTnT and NT-proBNP predict 30-day in-hospital mortality.

Introduction

Dyspnoea is a common symptom affecting 25% of patients seen in the ambulatory setting; complicating comorbidities can pose difficulties in the differential diagnosis [1]. A large cohort study estimated dyspnoea represented 5.2% of Emergency Department (ED) presentations and was responsible for 11.4% of ward admissions with an in-hospital mortality of 6% [2]. The differential diagnosis involves pulmonary and cardiac candidates; methods to distinguish between these have involved pulmonary function tests (FEV1 and dyspnoea differentiation index) [3]; later interest had revolved around NT-proBNP; a cardiac etiology of dyspnoea was found to have a significantly poorer prognosis than non-cardiac dyspnoea [4]. Survival curves differed, based on cut-points of 100 and 400 pg/ml, with three cohorts with different longer term survival [4]. Few published studies have stratified for comorbidity and acute illness severity that are the prime drivers of early in-hospital mortality [5].

We have previously reported that a positive troponin (hscTnT) predicts mortality in unselected general medical admissions [6, 7]. Furthermore there is a semiquantitative relationship with higher levels predicting worse outcomes [6]. NT-pro-BNP positivity and levels have similarly been shown to predict mortality in unselected general medical admissions [8]. The aim of the current study was to explore the utility of hscTnT and NT-pro-BNP in predicting outcomes in the specific subgroup of patients presenting with dyspnoea. We further evaluate resource implications of this testing strategy.

We have examined all dyspnoea admissions, over a 6 year period (2015-2020) to examine the current pattern of investigation, using NT-proBNP and hscTnT [6]. We related NT-proBNP and hscTnT to 30-day in-hospital mortality, length of stay (LOS), and number of investigations performed.

Methods

St James's Hospital, Dublin serves as a secondary care centre for emergency admissions in a catchment area with a population of 270,000 adults. All emergency medical admissions are admitted from ED to an Acute Medical Admission Unit (AMAU), the operation and outcome of which have been described elsewhere [9-12].

An anonymous patient database was employed, assembling core information from each clinical admission including details from the patient administration system, national hospital in-patient enquiry (HIPE) scheme, the patient electronic record and laboratory data. HIPE is a national database of coded discharge summaries from acute public hospitals in Ireland [13]. The International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) was used for diagnosis and procedure coding. Data included parameters such as date of birth, gender, area of residence, principal and up to nine additional secondary diagnoses, principal and up to nine additional secondary procedures, and admission and discharge dates. Additional information cross-linked and automatically uploaded to the database includes physiological, haematological, and biochemical parameters. This study includes all emergency medical admissions, including those admitted to ICU and HDU, in the 5 years between 2015 and 2020.

We examined the ED final 'sign-off' diagnosis recorded for all emergency medical admissions. A complete list of the possible 200 diagnoses is listed in Appendix 1.

We have previously derived and applied an Acute Illness Severity Score (AISS) [14], predicting 30-day in-hospital mortality from parameters recorded in the ED [15]. We further adjusted for comorbidity as described previously [16]. In addition, blood culture categories of 1) no blood culture request 2) negative blood culture and 3) positive blood culture were identified and used as an adjustor in the multivariable logistic regression model [17].

Descriptive statistics were calculated for background demographic data, including means/standard deviations (SD), medians/inter-quartile ranges (IQR), or percentages. Comparisons between categorical variables and mortality were made using chi-square tests. We adjusted the outcome computation (30-day in-hospital mortality) for other known predictor variables including AISS [14, 18], Comorbidity Score [16, 19] and blood culture status [17]. We employed a logistic model with robust estimate to allow for clustering; the correlation matrix thereby reflected the average discrete risk attributable to each of these predictor variables [14].

Logistic regression analysis identified potential mortality predictors and then tested those that proved to be significant univariate predictors ($p<0.1$ by Wald test) to ensure that the model included all variables with predictive power. We used the margins command in Stata to estimate and interpret adjusted predictions for sub-groups, while controlling for other variables such as time, using computations of average marginal effects. In the multivariable logistic regression model, we adjusted univariate estimates of effect, using the previously described outcome predictor variables.

We related either or both hscTnT or NT-proBNP test requests to LOS. Number of investigations/procedures was calculated by summing physiotherapy, speech & language, dietetics, social work, occupational therapy and psychiatric attendance and interventions including ventilation, bronchoscopy, GI endoscopy/colonoscopy and coronary angiography. This then was regressed against hospital LOS, using zero truncated Poisson regression, by the hscTnT or NT-proBNP request subsets.

Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated for those predictors that significantly entered the model ($p<0.10$). Statistical significance at $P<0.05$ was assumed throughout. Stata v.17 (Stata Corporation, College Station, Texas) statistical software was used for analysis.

Results

Patient Demographics

There were a total of 49,965 emergency medical admissions in 29,953 patients over the 6 year study period. The proportion of males was 49.7%. The median (IQR) length of stay (LOS) was 5.0 (2.3, 9.8) days. The median (IQR) age was 66.0 (48.1, 79.9) years, with the upper 10% boundary at 87.5 years.

Patient characteristics related to a dyspnoea presentation

Of the 49,965 presentations, 7,087 (14.2%) were due to dyspnoea, Table 1. Patients with a dyspnoea presentation were older at 69.6 years (56.1, 80.2) vs. 64.8 years (46.2, 79.3) and had a longer hospital LOS at 6.4 days (3.2, 12.6) vs. 5.0 days. (2.0, 11.1). Their 30-day in-hospital mortality was higher at 7.4% vs 4.1% ($p<0.001$). They had higher illness severity (AISS Category V/VI – 70.5% vs. 57.6%) and Comorbidity Score (>=6 points 41.1% vs. 29.8%) and more positive blood cultures (4.6% vs. 3.5%).

Table I: Emergency Medical Admissions (2015-2020) by Dyspnoea Status

	Others (N=42,878)	Dyspnoea (N=7,087)	p-value
Age (years)			
Median (Q1, Q3)	64.8 (46.2, 79.3)	69.6 (56.1, 80.2)	<0.001
Length of Stay (days)			
Median (Q1, Q3)	5.0 (2.0, 11.1)	6.4 (3.2, 12.6)	0.11
Gender			
Male	21646 (50.5%)	3470 (49.0%)	0.02
Female	21232 (49.5%)	3617 (51.0%)	
30-day in-Hospital Mortality			
Alive	41100 (95.9%)	6564 (92.6%)	<0.001
Dead	1778 (4.1%)	523 (7.4%)	
Acute Illness Severity Score			
1	1730 (4.3%)	124 (1.8%)	<0.001
2	3247 (8.0%)	290 (4.2%)	
3	5303 (13.1%)	564 (8.1%)	
4	6949 (17.1%)	1076 (15.5%)	
5	7958 (19.6%)	1337 (19.2%)	
6	15441 (38.0%)	3571 (51.3%)	
Comorbidity Score			
<6	30084 (70.2%)	4181 (59.0%)	<0.001
6	11285 (26.3%)	2507 (35.4%)	
10	1366 (3.2%)	360 (5.1%)	
13	137 (0.3%)	39 (0.6%)	
16	6 (0.0%)	0 (0.0%)	
Charlson Index			
0	22287 (54.0%)	1786 (27.1%)	<0.001
1	10707 (25.9%)	2662 (40.4%)	
2	8304 (20.1%)	2135 (32.4%)	
Sepsis Group			
1	33965 (79.2%)	5015 (70.8%)	<0.001
2	7425 (17.3%)	1745 (24.6%)	
3	1488 (3.5%)	327 (4.6%)	

Troponin (hscTnT) and NT-proBNP testing in different dyspnoea cohorts

One would anticipate a significant level of hscTnT requests; our prior expectations of overall hscTnT and NT-proBNP requests were 24.4 % and 14.0% respectively [6]. However, for the hscTnT assay, although the request level was about the anticipated level overall at 39.5%, it is noteworthy the dyspnoea had a much higher 30-day in-hospital mortality than the non-dyspnoea cohort (6.4% vs. 3.4%). Within the defined cohorts, overall request levels were highest for the elderly >70 years (53.9%) and underlying cardiac disease (61.6%). The highest mortality rates occurred where dyspnoea triggered a hscTnT request in conjunction with age >70 years (12.4%) or respiratory disease (13.0%).

For NT-proBNP, compared with all acute medicine admissions of 14.0%, dyspnoea triggered a higher request volume at 41.8%. Within the defined cohorts, overall request levels were highest for the elderly >70 years (52.5%) and underlying cardiac disease (65.6%). The highest mortality rates, however, occurred where dyspnoea triggered a NT-proBNP request in combination with age >70 years (11.8%) or respiratory disease (14.4%).

Troponin (hscTnT) levels and 30-day in-hospital per admission mortality

The relationship between 30-day in-hospital mortality and the hscTnT level was curvilinear and predictive for both a dyspnoea presentation - model adjusted OR 1.24 (95%CI: 1.16, 1.33) and a non-dyspnoea presentation OR 1.29 (95%CI: 1.25, 1.34), Figure 1A. The model predicted 30-day in-hospital mortality was 6.7% (95%CI: 5.5, 8.0) for dypsnoea vs. 5.0% (95%CI: 4.7, 5.4) for non-dyspnoea. This was due to higher illness severity and comorbidity; after adjustment, dyspnoea 4.3% (95%CI: 3.4, 5.1) and non-dyspnoea presentations 4.1% (95%CI: 3.7, 4.5) had similar outcomes. Higher hscTnT levels predicted a worse outcome in dyspnoea.

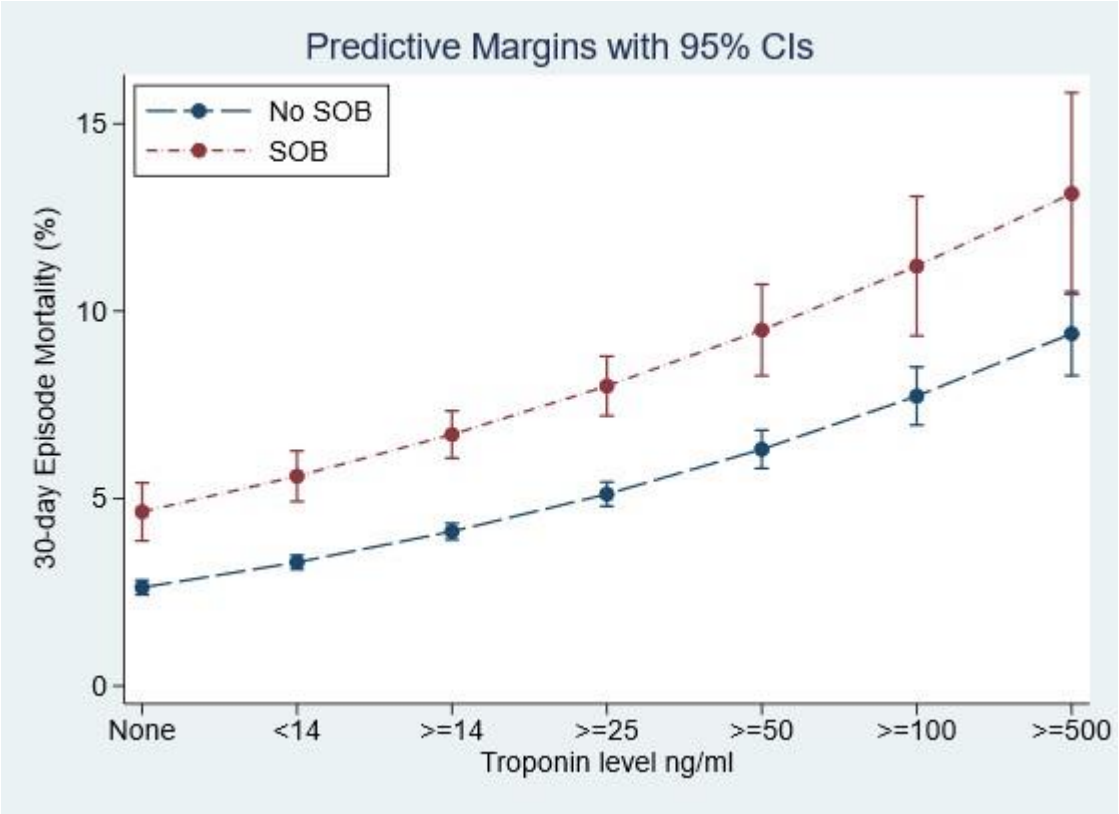

Figure 1: Relationship between episode hscTnT levels and 30-day in-hospital mortality, for emergency presentations by dyspnoea status.

NT-proBNP levels and 30 day in-hospital per admission mortality

The relationship between 30-day in-hospital mortality and the NT-proBNP level was linear and predictive both for dyspnoea, model adjusted OR 1.11 (95%CI: 1.08, 1.15), and non-dyspnoea presentations, OR 1.12 (95%CI: 1.06, 1.18), Figure 2. After adjustment for major risk predictors, the mortality outcome of dyspnoea vs. non-dyspnoea was similar – 30-day in-hospital mortality 4.6% (95%CI: 3.7, 5.5) vs. 4.3% (95%CI: 3.9, 4.7). The essential parallel relationships for both hscTnT and NT-proBNP, between dyspnoea and non-dyspnoea cohorts when adjusted for baseline difference in acute illness severity and comorbidity scores would suggest that cut-points, as sometimes recommended are somewhat artefactual, whereas the risk appears essentially curvilinear.

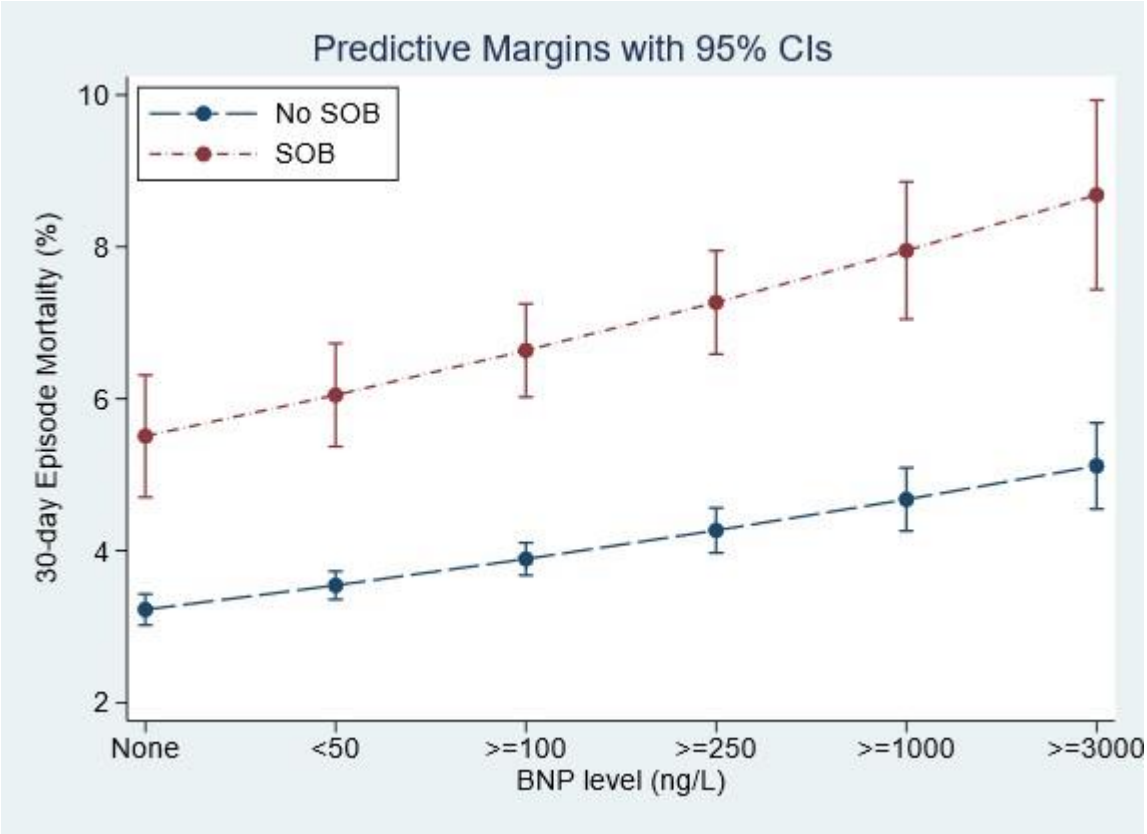

Figure 2: Relationship between episode NT-proBNP assay level and 30-day in-hospital mortality, for clinical presentations by dyspnoea status.

Pattern of Investigation and LOS in relation to hscTnT and NT-proBNP testing

There was clearly a linear relationship between the hospital LOS and the number of procedures/interventions, adjusted for case complexity IRR 1.30 (95% CI: 1.29, 1.30), but low prediction based on whether hscTnT or NT-proBNP tests were requested 1.04 (95% CI: 1.03, 1.05) (Figure 3).

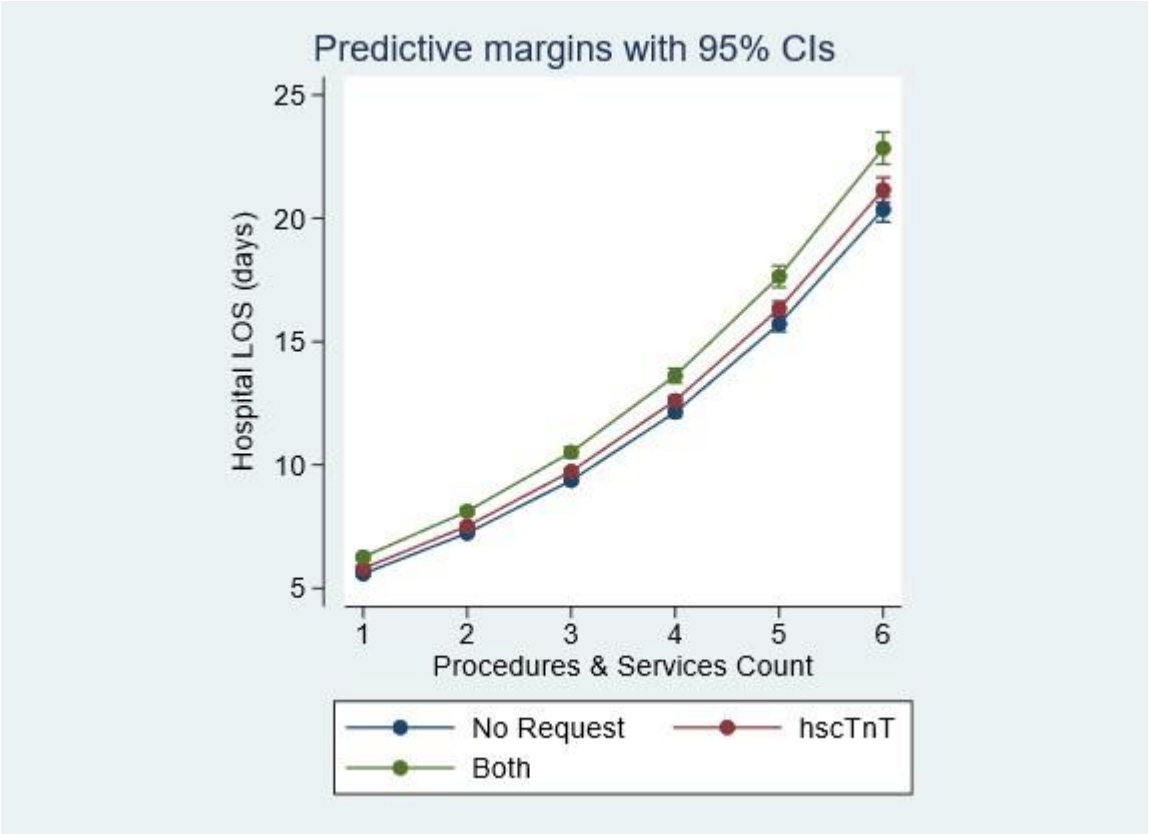

Figure 3: Relationship between hscTnT, NT-proBNP, and hospital LOS and procedure count.

Discussion

Dyspnoea represents a major workload for both the ED and Acute Medicine. Our model predicted a 30-day mortality of 6.7% for a dyspnoea admission vs. 5.0% for a non-dyspnoea admission. This was due to higher illness severity and comorbidity - after adjustment the differences did not persist (4.3% vs 4.1%). A large cohort study provided a similar estimate for the in-hospital dyspnoea mortality estimated at 6% [2]. Our data further suggests that dyspnoea, from an aetiology point of view, is more likely to represent underlying respiratory than cardiovascular disease.

We have previously demonstrated that hscTnT and NT-pro-BNP predict outcomes in unselected general medical admissions [6, 8]. While one might anticipate that these biomarkers would be useful and prognostic in dyspnoea, the converse could also be true in this more select population. Therefore the current study adds to our previous work by demonstrating the predictive value of hscTnT and NT-pro-BNP in patients presenting with dypsnoea. Troponin has been identified as prognostic in a range of different (mainly cardiac) clinical conditions . In 105,338 hospitalized heart failure admissions, Peacock et al [20] found a positive troponin test predicted mortality (- adjusted OR 2.55). In surgical ICU patients, even moderately elevated troponin I levels –were associated with a higher mortality rate and longer hospital and ICU LOS [21]. A study in acute respiratory distress syndrome reported a high prevalence of elevated cardiac markers [22] and an associated increased 60-day mortality and organ failure.

Unlike the many studies on troponin, there has been less publication on the impact of NT-pro-BNP in day-to-day clinical settings, despite recommendations regarding the need to study this [23]. However, studies have looked at BNP and NT-pro-BNP in the dyspnoeic patient suggesting such testing improved diagnostic accuracy and reduced overall costs [24]. In both acute and chronic heart failure, a meta-analysis found a high degree of diagnostic accuracy for both BNP and NT-pro-BNP assays [25], with for BNP sensitivity of 93.5% and positive likelihood ratio of 2.2 and for NT-pro-BNP sensitivity of 90.4%, and positive likelihood ratio of 1.8. Our earlier finding was that very elevated NT-pro-BNP level >5000 ng/L predicted mortality [26] but the dose-response relationship that any specific cut-off is somewhat arbitrary.

There is always concern regarding excessive unwarranted investigation; for example, the clinical utility of elevated troponin levels outside the chest pain spectrum is uncertain; concern has been expressed about frequent 'inappropriate' troponin tests [27]. However, it is not appreciated that requesting a test may be associated with unintentional risk allocation; sepsis is a frequent concern in emergency medical patients with a blood culture request in over 20% [17]. The 30-day mortality outcome in a dyspnoea presentation by blood culture request status of no request, negative culture or positive culture was 3.6%, 13.6% and 18.7%. Clearly a blood culture request, irrespective of the result was prognostic. In the dyspnoea patient, either a troponin or NT-proBNP test defined a higher risk category. It is difficult to argue overuse of laboratory tests, when firstly there is clear separation of outcomes between those tested and non-tested, and there is a linear relationship between the test level and 30-day mortality.

While we have evaluated a large number of observations in a comprehensive cohort of admissions there are some limitations inherent in our work. It is possible that residual unmeasured confounders exist which are not accounted for in our multivariable modelling. This was a single center study and our findings will need replication in other settings and cohorts to determine their external validity. It is important to recognize that our study design evaluated patients admitted under the general/acute medical teams and that patients admitted under other services, such as cardiology, were not evaluated in this analysis.

In conclusion we have demonstrated that dyspnoea presentations are associated with increased mortality. NT-proBNP and hscTnT levels at presentation were predictive of mortality. These findings may assist clinicians in risk prognostication.

Conflicts of Interest:

All authors declare that there are no conflicts of interest.

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