Original Article

Blood Culture and Troponin Testing in Suspected Bacteraemic Admissions - Example of Risk Stratification Based on Clinical Testing

R Conway, D Byrne, D O'Riordan & B Silke

Abstract

Aim: To investigate the clinical predictive value of troponin (hscTnT) and blood culture testing.

Methods: We examined all medical admissions from 2011-2020. Prediction of 30-day in-hospital mortality, dependent on blood culture and hscTnT requests/results, was evaluated using multiple variable logistic regression. Length of stay was related to utilization of procedures/services with truncated Poisson regression.

Results: There were 77,566 admissions in 42,325 patients. With both blood cultures and hscTnT requested, 30-day in-hospital mortality increased to 20.9% (95%CI: 19.7, 22.1) vs 8.9% (95%CI: 8.5, 9.4) for blood cultures alone and 2.3% (95%CI: 2.2, 2.4) with neither. Blood culture 3.93 (95%CI: 3.50, 4.42) or hsTnT requests 4.58 (95%CI: 4.10, 5.14) were prognostic.

Conclusion: Blood culture and hscTnT requests and results predict worse outcomes.

Keywords

Troponin levels, Emergency Medical Admissions, Resource Utilization

Introduction

The emergency medical admission bears a substantial risk; clinical outcomes such as 30-day in-hospital mortality have improved over time.[1-4] Such quality improvement has been variously attributed to restructuring of operational systems or improved patient flow;[5, 6] structural innovations of the AMAU process[1-3] and increased direct consultant participation.[7] Resources are inevitably constrained and clinicians may have to manage austerity; in Ireland the national emergency from 2008 necessitated healthcare budgetary reductions estimated at approximately 22%[8] and sustained for a decade. Quality improvement in such circumstance requires a reliable evidence base, so that scarce resources may be deployed to areas of greatest clinical need; analysis of routinely collected clinical data on hospital admissions may inform these decisions.

Admission laboratory parameters can assist risk assessment; derangement of haematology or biochemical values is an index of illness severity, with extent of homeostatic failure of prognostic significance. Prytherch et al.,[9] Froom and Shimoni[10] and Hucker,[11] developed algorithmic scores based on admission laboratory data which are predictive of short-term hospital mortality. Our own initial work[12] and the later notable contribution of Froom and colleagues[13] yielded high AUROC predictive models, based on routinely collected admission data. However, whilst some laboratory data is routinely collected, there is also conditional testing, where presenting symptoms, clinical profile or a clinical examination triggers the request. Blood culture or troponin (hscTnT) testing would likely be included in this category; what is not adequately appreciated is the extent to which such conditional testing results in the creation of subgroups, stratified by first the test request and secondly the test result.

Cardiac troponins have been found predictive in a variety of situations apart from acute coronary syndromes such as acute heart failure,[14] chronic heart failure,[15] renal insufficiency,[16] non-cardiac surgery[17] and sepsis.[18] Sepsis and bacteraemia are common in emergency medical admissions with a blood culture requested in over 20% of all our acute admissions.[19] However, with a non-routine test, such as where a blood culture or hscTnT follows on a clinical assessment, due to the risk stratification one cannot assume that a negative result is equivalent to no test request. The different risk characteristics[19, 20] of subgroups based on the test request and consequent stratification, may lead to divergent clinical trajectories, different use of procedures, services and clinical outcomes.

The purpose of this study was to evaluate in this context blood culture and hscTnT testing in emergency medical admissions. We investigated whether such testing led to unanticipated risk stratification, with divergence in hospital length of stay (LOS), resource utilization and ultimately clinical outcomes dependent on either the request for the test and/its result.

Methods

Background

St James's Hospital, Dublin serves as a secondary care centre for emergency admissions in a catchment area

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with a population of 270,000 adults. All emergency medical admissions are admitted from the Emergency Department (ED) to an Acute Medical Admission Unit (AMAU), the operation and outcome of which have been described elsewhere.[2, 4, 21-23]

Data collection

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.[24, 25] The International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) was used for both diagnosis and procedure coding. Data includes the unique hospital number, admitting consultant, 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 in the 10 years between 2011 and 2020.

Troponin measurements

In January 2011, our institution introduced a hscTnT assay to replace a 4th-generation cardiac troponin assay. For the purposes of this study, we defined troponin-negative as hscTn <25 ng/L and troponin-positive as hscTn ≥25 ng/L.

Risk Predictors

Derangement of admission biochemical parameters may be utilised to predict clinical outcome. We have previously derived and applied an Acute Illness Severity Score (AISS),[12] predicting 30-day in-hospital mortality from parameters recorded in the ED (26). A weighted age adjusted score was derived; six risk groups (I–VI) were identified with cut-points for 30-day in hospital mortality set at 1, 2, 4, 8 and 16%. We further adjusted for comorbidity as described below. 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 multiple variable logistic regression model.[27]

Comorbidity Score

Patient morbidity was assessed by a Comorbidity Score[28] published in 2014, which was further adjusted by additional information collected by our information system since.[29] To devise the score, we searched ICD codes that captured chronic physical or mental health disorders that limit people in activities that they generally would be expected to be able to perform were grouped according to the following ten systems: (i) cardiovascular, (ii) respiratory, (iii) neurological, (iv) gastrointestinal, (v) diabetes, (vi) renal, (vii) neoplastic disease, (viii) others (including rheumatological disabilities), (ix) ventilatory assistance required and (x) transfusion requirement. In addition, we searched our hospital's other databases for evidence of diabetes (Diamond database),[30] respiratory insufficiency (FEV1 <2L), troponin status (high sensitivity troponin ≥25 ng/L),[31] low albumin (<35 G/dL) and anaemia (haemoglobin levels <10 G/dL) or chronic renal insufficiency - MDRD < 60 mL/min*1.73 m2.[32] Each component of the score was then weighted according to 30-day in-hospital mortality.

Statistical methods

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,[12, 33] Comorbidity Score[34, 35] and blood culture status.[27] 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.[12]

Logistic regression analysis identified potential mortality predictors and then tested those that proved to be significant univariate predictors ($p<0.1$ by Wald test. The dependent variable of the hospital length of stay (LOS) is restricted to certain values; the predictor variables were therefore regressed against LOS using the truncated Poisson model. We used robust standard errors for the parameter estimates, as recommended by Cameron and Trivedi (36). The Poisson regression coefficients are the log of the rate ratio: one can interpret the coefficients in terms of incidence rate ratios (IRR). We used the margins command in Stata to estimate and interpret adjusted subgroup predictions, controlling for other variables, using computations of average marginal effects. Margins are statistics calculated from predictions of a previously fitted model at fixed values of some covariates and averaging or otherwise over the remaining covariates..

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 77,566 emergency medical admissions in 42,325 patients over the 10 year study period (2011-2020). This included patients admitted directly into the Intensive Care Unit or High Dependency Unit. The proportion of males was 49.8%. The median (IQR) LOS was 5.5 (2.2, 12.1) days. The median (IQR) age was 66.8 (47.1, 79.5) years, with the upper 10% boundary at 86.7 years. Blood cultures were requested in 24.4% of admissions, with 16.1% positive

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Table 1. Multiple Variable Model Predictors of 30-day In-hospital Mortality

	No Culture (N = 58,651)	Negative (N = 14,939)	Positive (N = 2,874)	p-value
Age *	65.7 (47.3, 79.5)	65.6 (45.7, 79.4)	68.5 (49.7, 81.1)	<0.001
Hospital LOS	4.6 (1.9, 9.8)	8.9 (4.5, 20.7)	14.0 (6.1, 36.7)	<0.001
Male	28604 (48.8%)	7700 (51.5%)	1539 (53.5%)	<0.001
Female	30047 (51.2%)	7239 (48.5%)	1335 (46.5%)	
Survive to discharge	57107 (97.4%)	13368 (89.5%)	2408 (83.8%)	<0.001
Any Hospital death	1544 (2.6%)	1571 (10.5%)	466 (16.2%)	
Illness Severity				
1	2267 (4.1%)	332 (2.2%)	27 (1.0%)	<0.001
2	4387 (7.9%)	815 (5.5%)	90 (3.2%)	
3	7375 (13.3%)	1332 (9.0%)	151 (5.3%)	
4	9788 (17.6%)	1888 (12.8%)	320 (11.3%)	
5	11192 (20.1%)	2410 (16.3%)	418 (14.7%)	
6	20576 (37.0%)	7986 (54.1%)	1835 (64.6%)	
Comorbidity Score				
<6	41846 (71.3%)	8623 (57.7%)	349 (12.1%)	<0.001
6	15429 (26.3%)	5619 (37.6%)	1380 (48.0%)	
10	1312 (2.2%)	665 (4.5%)	914 (31.8%)	
13	64 (0.1%)	32 (0.2%)	215 (7.5%)	
16	0 (0.0%)	0 (0.0%)	16 (0.6%)	
MDC4 Respiratory	46,581 (79.4%)	9,733 (65.2%)	2,063 (71.8%)	<0.001
	12,070 (20.6%)	5206 (34.8%)	811 (28.2%)	
MDC5 Cardiovascular	47,381 (80.8%)	13,593 (91.0%)	2,585 (89.9%)	<0.001
	11,270 (19.2%)	1,346 (9.0%)	289 (10.1%)	
MDC1 Neurology	48,501 (82.7%)	13,438 (90.0%)	2572 (89.5%)	<0.001
	10,150 (17.3%)	1,501 (10.0%)	302 (10.5%)	

* Median (Q1, Q3)

and 83.9% negative. The 30-day in-hospital mortalities for the three groups of no blood culture, culture negative and culture positive, per admission were 2.2% (95% CI: 2.1, 2.3), 9.3% (95% CI: 8.8, 9.8) and 14.3% (95% CI: 12.8, 15.9) respectively and per unique patient (prior admissions excluded) were 4.1% (95% CI: 3.9, 4.3), 16.8% (95% CI: 15.9, 17.7) and 25.9% (95% CI: 23.3, 28.5).

Patients with a positive blood culture were older at 68.5 years (IQR 49.7, 81.1) than patients with a negative blood culture at 65.5 years (IQR 45.7, 79.4) or no blood culture requested at 65.7 years (IQR 47.3, 79.5). Those with either a positive blood culture at 14.0 days (IQR 6.1, 36.7) or a negative blood culture at 8.9 days (IQR 4.5, 20.7) had a longer LOS compared with no blood culture request at 4.6 days (IQR 1. 9, 9.8). The 30-day in-hospital mortality per admission was higher for those with either a positive blood culture,14.3% (95% CI: 12.8, 15.9) or negative blood culture, 9.3% (95% CI: 8.8, 9.8) , compared with no blood culture request 2.2% (95% CI: 2.1, 2.3). Patients with a positive blood culture had higher Illness Severity (Gr. IV – VI) and Comorbidity (Score > 6 points) compared with a negative or no blood culture request (Table 1).

Clinical Presentations followed by a Blood culture request

The ED presenting symptoms of all clinical presentations between 2015 and 2020 inclusive (n = 49,965) were available. The presenting symptom of the subsequent blood culture cohort were, in descending order, dyspnoea (18.9%), non-specific (17.2%), pain (8.7%) and infection (4.8%). Major disease categories (MDCs) were Neurology (3.2%), Gasteroenterology (2.1%), Respiratory (1.9%) and Cardiovascular (1.1%). Injury accounted for 2.0%; cumulatively these categories in total accounted for 91.3% of these presentations, where the admission triggered a blood culture request.

In terms of prediction of an in-hospital death, the most important consideration was underlying cardiovascular disease - OR 5.69 (95% CI: 3.38, 9.58) or a (possibly related) dyspnoea presentation OR 1.23 (95% CI: 1.03, 1.47). Other presentations such as non-specific/respiratory/neurology did not predict the outcome, whereas many such as pain or infection had a better than average prognosis (Table 2).

Table 2. Multiple Variable Logistic Regression Prediction of Sepsis Testing

Variable	Odds Ratio	Std. Err.	Z	P>|z|	[95% Conf. Interval]	
Dyspnoea	1.23	0.11	2.3	0.02	1.03	1.47
Non-Specific	0.94	0.10	-0.6	0.57	0.77	1.16
Pain	0.56	0.10	-3.2	0.00	0.39	0.80
Infection	0.46	0.11	-3.2	0.00	0.29	0.74
Neurological	0.80	0.33	-0.6	0.58	0.35	1.80
Respiratory	0.81	0.24	-0.7	0.47	0.46	1.44
Cardiovascular	5.69	1.51	6.5	0.00	3.38	9.58
High Acuity	2.69	0.23	11.7	0.00	2.28	3.18
High Comorbidity	1.15	0.01	12.9	0.00	1.13	1.18

Blood culture request and result as prognostic indicators

By univariate analysis, a blood culture OR 3.93 (95% CI: 3.50, 4.42) or a Troponon test (hscTnT) - OR 3.73 (95% CI: 3.33, 4.12) were each prognostic for 30-day in-hospital mortality. Were both tests requested, then the model predicted 30-day in-hospital mortality would be 20.9% (95% CI: 19.7, 22.1) compared with 8.9% (95% CI: 8.5, 9.4) for any blood culture request or no test request 2.3% (95% CI: 2.2, 2.4). A positive blood culture result would have greater probability of an adverse outcome OR 6.44 (95% CI: 5.59, 7.41) than a negative result - 4.06 (95% CI: 3.73, 4.42) - both obviously were major adverse predictors. In the full model, the predicted difference in outcomes, between

no blood culture, negative and positive results for 30-day in-hospital mortality is evident (Figure 1). In the multiple variable model (using variables as described above) the blood culture - OR 1.98 (95% CI: 1.85, 2.11) or hscTnT test prediction - OR 1.85 (95% CI: 1.69, 2.03) were attenuated although both were very significant (p<0.001). The attenuation was driven by major predictors such as the Illness Severity OR 2.74 (95% CI: 2.48, 3.02) or MDCs of Neurology OR 1.98 (95% CI: 1.72, 2.29) or Respiratory Disease OR 1.53 (95% CI: 1.38, 1.70).

hscTnT test frequency in different risk cohorts

We determined the frequency of hscTnT request in various cohorts, including those with high AISS, Comorbidity Score, Sepsis status, and MDCs (Table 3). Overall, the frequency of hscTnT testing was 24.5%, but ranged from a low of 15.2% in neurologic presentations, 38.5% for cardiovascular presentations and 57.1% in those who subsequently died. In the blood culture cohort, the hscTnT request frequency was higher (34.4% vs. 22.0%: p<0.001).

A hscTnt test would, as a univariate, predicted an adverse outcome, generally in all admissions OR 4.63 (95% CI: 4.28, 5.01) or specifically in blood culture tested individuals - 4.58 (95% CI: 4.10, 5.14). In the full model, the hscTnT risk prediction in the blood culture cohort was reduced - OR 2.01 (95% CI: 1.77, 2.28); the model predicted an increase in 30-day in-hospital mortality from 7.5% (95% CI: 6.9, 8.0) with no hscTnT to 31.1% (95% CI: 12.3, 13.9) were a hscTnT test was performed. An elevated hscTnT (i.e. >= 25 ng/L) was returned in 23.6% of the blood culture cohort; the model predicted 30-day in-hospital mortality would increase from 7.3% (95% CI: 6.8, 7.8) with hscTnT < 25 ng/L to 15.1% (95% CI: 14.1, 16.2) if hscTnT result was >= 25 ng/L.

Blood culture or hscTnT testing and subsequent hospital LOS

There is concern that testing may trigger additional further procedures and prolong a hospital episode unnecessarily. We calculated the number of events recorded on our hospital system including allied service utilization (physiotherapy, speech & language and dietetics), social, occupational therapy and psychiatric attendance and interventions including ventilation, bronchoscopy, GI endoscopy/colonoscopy and coronary angiography. We regressed the sum of these against hospital LOS, using truncated Poisson regression, by the blood culture status (no request, negative or positive result). There was clearly a linear relationship between the hospital LOS and the number of such procedures/interventions; adjusted for case complexity and hscTnT status, the number of subsequent procedures/interventions correlated directly (p<0.001) with the hospital LOS – the latter was correlated with both the blood culture IRR 1.34 (95% CI: 1.32, 1.36) and the hscTnT status IRR 1.17 (95% CI: 1.16, 1.19). The dependency of LOS on requested procedures and service, by blood culture status, is illustrated in Figure 2.

Table 3. Troponin test frequency in different cohorts

Cohort	Frequency (%, n)	30-day Mortality* (95% CI)
Overall	24.5% (19,010/77,566)	7.0% (6.8%, 7.3%)
Blood culture request	32.4% (6136/18,915)	18.0% (17.2%, 18.9%)
No blood culture request	22.0% (12,874/58,651)	4.1% (3.9%, 4.3%)
Blood Culture Negative	33.3% (4975/14,939)	16.8% (15.9%, 17.7%)
Blood Culture Positive	40.4% (1161/2874)	25.9% (23.3%, 28.5%)
Died	57.1% (2044/3581)	

calculated on per patient basis

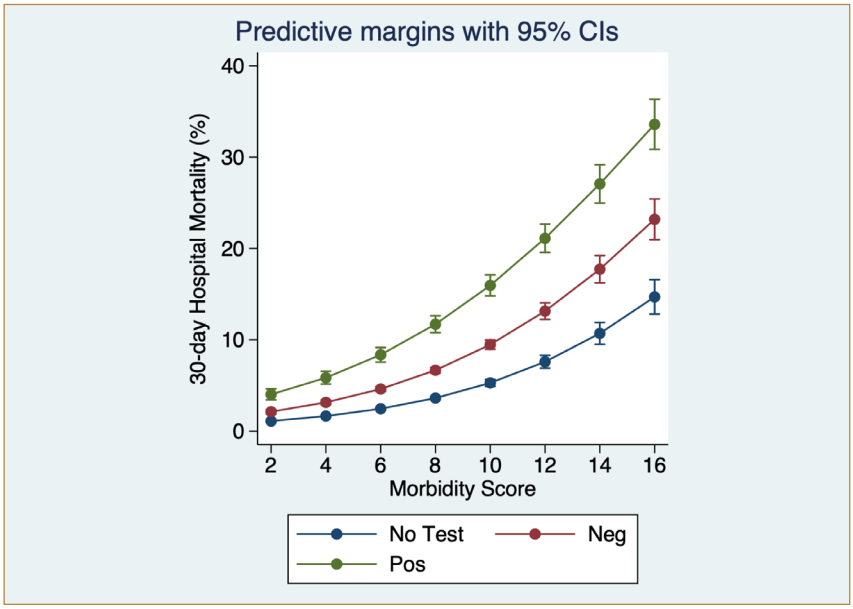

Figure 1. Curvilinear relationship between Comorbidity Score and 30-day in-hospital mortality, by blood culture status. The Comorbidity Score was < 6 points in 66.5%, between 6 – 10 in 29.3% with only 3.8% scored at > 10 points.

Discussion

Our study has shown that both the decision to perform a blood culture or a hscTnT test risk stratifies; the subgroups possessed different hospital outcomes, LOS and resource utilization. These blood culture or hscTnT tests are not routine but follow a clinical assessment; it is the decision to request that is fundamental to the risk stratification. A negative test result is not equivalent to no test request; although 83.9% of blood culture test proved negative, the 30-day hospital episode mortality for the negative blood culture cohort at 9.3% (95% CI: 8.8, 9.8) was much higher than where there had been no blood culture request 2.2% (95% CI: 2.1, 2.3). Similarly, a negative hscTnT was returned in 76.4% of the blood culture cohort – however in the blood culture negative cohort a hscTnT test request would increase

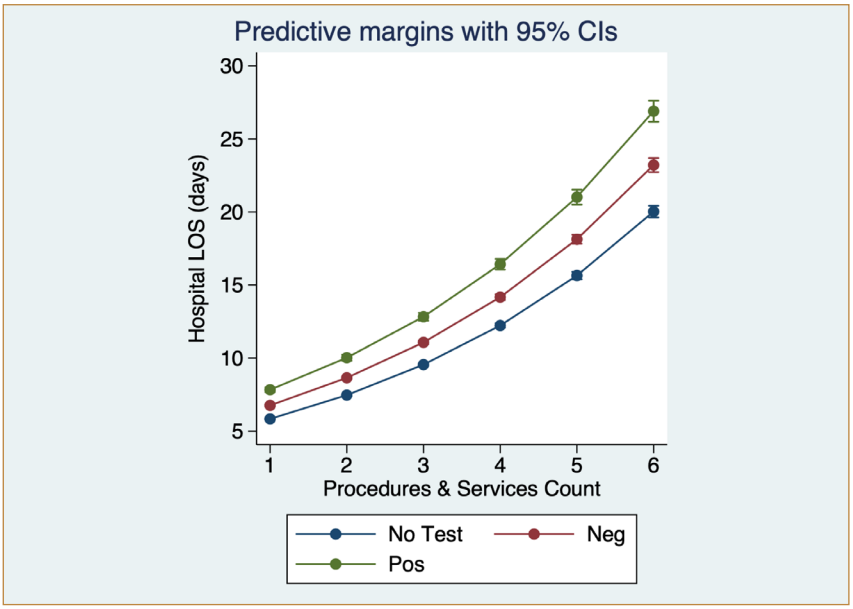

Figure 2. Hospital Length of Stay and Resource Utilization related to blood culture request from the truncated Poisson regression model. A longer hospital LOS and more service/procedure utilization, showed blood culture status dependency.

the model predicted 30-days hospital mortality from (no request) 11.0 % (95% CI: 9.1, 12.8) to 18.5% (95% CI: 16.0, 21.0). The ORs for both blood culture or hscTnT tests, as univariate prognostic predictors in acute medical admissions, were large and remained significant (albeit attenuated) after adjustment for other risk predictors.

Previous work on troponin in sepsis included a meta-analysis, of 926 patients with sepsis of whom nearly 70% had elevated cardiac troponin levels; the latter had more than double the mortality rate (31% vs 71%, $p < 0.0001$).[18] Similarly another group found that elevated troponin levels were prognostic with higher mortality (32.2%vs 13.6%, $p < 0.0001$).[37] However, the data in sepsis has not been consistent with some studies failing to confirm that troponin was prognostic.[38] Of course, the numbers in some studies are relatively small and chance may determine negative results. In the emergency medical admission there are patients with quite different case complexities; prognosis is a dependent function of case complexity with illness severity and the co-morbidity burden being the principal determinants of mortality.[39] Our data indicates that both the blood culture and hscTnT test request, and the test result (culture positive vs. negative and the returned hscTnT value) define risk groups with different clinical trajectories and outcomes.

In terms of volume of testing, there are some data suggesting that unnecessary troponin testing may lead to unnecessary hospitalizations, cardiac monitoring, cardiac consultations and possible coronary angiography.[40] Wilson et al.[41] have suggested overuse of troponin testing in the healthcare system; with the majority of troponin measurements being single, not serial (64%). Moreover, few of such patients have a primary or secondary diagnosis of acute myocardial infarction (AMI), the majority (79%) of elevated troponin values were associated with primary diagnoses other than AMI. However, recommendations to restrict troponin testing to clinical presentations with chest pain or with ischemic electrocardiographic changes[40] would be very restrictive (our cardiac presentations at 8.6%) and a considerable distance from our clinical colleagues contemporary practice of 24.4%, much less the level of testing at >30% in sepsis patients. The 'appropriate' level of troponin testing in unselected emergency medical presentations is not clear – possibly the negative/positive test ratio might serve as an index. However, our data showing the positive hscTnT test rate (>25 ng/L) at 15.9% generally and in bacteraemia at 21.8% provides some context.

Of course, potentially any test that is the result of a clinical assessment or 'intuitive' decision may define risk dividing patients into lower and higher on the basis of a test request, this applies both to a blood culture and hscTnT test,[19, 20] where the test result categorises groups with different risk characteristics. More testing may subsequently be required after the blood culture or troponin testing, as the clinical 'intuitive' decision to 'test' or 'not test' selects cohorts with different risk characteristics. Such cohorts may have different case complexity; resource utilization increases as a dependent function of case complexity with the number of investigations/services a reflection of the embedded risk profile of the admitted population.[39] The linear relationship between the LOS and the services/investigations performed may be intuitively obvious – that the hospital LOS is largely a function of case complexity and the number of investigations/services an objective reflection of such.[42]

Our study is notable for several strengths including the large number of included patients and the comprehensive assessment of clinically relevant data on possible risk predictors. There are of course also limitations to any study design. We have demonstrated independent associations when accounting for known measurable risk predictors; it is possible that residual unmeasured confounders remain. While our study is large, it is based in a single institution and the external validity of our findings requires confirmation. Finally, our study reports on general medical admissions and did not include patients admitted to other services including cardiology; given the known strong prognostic value of troponin in cardiology patients however we would view this as a strength as it enables us to better identify potential relationships in non-cardiology conditions.

In conclusion, we have demonstrated that the performance and results of blood cultures and hscTnT are predictors of outcome in medical admissions.

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Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Conway R, Byrne D, O'Riordan D, Silke B.

Availability of data and materials

No further data is available for sharing. All pertinent data has been published in this manuscript.

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Conflicts of Interest

All authors declare that there are no conflicts of interest

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