ORIGINAL RESEARCH

Common laboratory tests predict imminent medical emergency team calls, intensive care unit admission or death in emergency department patients

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Abstract

Objective: To estimate the ability of commonly measured laboratory variables to predict imminent (within the same or next calendar day) medical emergency team (MET) calls, ICU admission or death.

Methods: We performed a retrospective observational study of ED patients. We estimated the ability of each laboratory variable or combination of variables together with patient age to predict imminent MET calls, ICU admission or death. We externally validated our findings in patients from a different hospital.

Results: We studied 160,341 batches in 71,453 ED patients (average age: 59.9 ± 22.1 years) for a total of 1 million individual measurements. There were 341 MET calls, 160 ICU admissions from the wards and 858 deaths. Multivariable modelling achieved a receiver operating characteristic area under the curve (ROC-AUC) of 0.69 (95% CI 0.63–0.74) for imminent MET call with prediction occurring a mean of 11.9 h before the call. Additionally, it achieved a ROC-AUC of 0.82 (95% CI 0.73–0.87) for imminent ICU admission. Finally, it achieved a ROC-AUC of 0.90 (95% CI 0.87–0.91) for imminent death. When tested using an additional 37,367 batches from a cohort of 21,430 ED patients from a second teaching hospital, the multivariate model achieved a ROC-AUC of 0.70 (95% CI 0.66–0.73) for imminent MET call, a ROC-AUC of 0.84 (95% CI 0.78–0.90) for imminent ICU admission. Finally, it achieved a ROC-AUC of 0.89 (95% CI 0.86–0.91) for imminent death.

Conclusions: Commonly performed laboratory tests can help predict imminent MET calls, ICU admission or death in ED patients. Prospective investigations of the clinical utility of such predictions appear desirable.

Key words: biochemistry, emergency department, laboratory, medical emergency team, mortality, outcome.

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Introduction

Among ED patients, some are at high risk of serious adverse events.1–4 The identification of such high-risk patients is important because their outcome has been shown to be worse if, instead of being directly admitted to the ICU, they are admitted to the general ward.5,6 Additionally, knowledge of which patients will require a medical emergency team (MET) review is likely to avoid MET activation delays, with their attendant increase in mortality.7,8 Finally, appreciation of which patients are likely to die would assist in preventing cardiac arrests, prioritising care or facilitating end-of-life discussions.9–12

Various attempts have been made to develop predictive systems for ED patients.2,4 However, such systems have been disease-specific,13–15 either based on the short-term application of ICU-developed illness severity scores,4 or based on selected physiological abnormalities assessed with vital sign acquisition.2,4 Other studies either have focused on a specific group of patients or have involved only hundreds of patients.16–18 When general studies have been performed in ED patients or patients just admitted to hospital,19–24 they have used clinical data to improve their predictive capability. This approach is clinically valuable25,26 but makes assessment of the independent value of laboratory data problematic. Other studies have not considered ED patients separately, or have not developed a predictive model. More importantly, none of these studies has focused on imminent death, ICU admission or MET review as the outcome of interest.

Identification of admitted ED patients at risk of serious adverse events is important. Accordingly, we performed a study to determine whether, in ED patients, commonly measured laboratory variables might serve as useful quantitative predictors of imminent major adverse events, such as MET call, ICU admission or death. In particular, we hypothesised that one or more laboratory tests or combinations of tests might have a fair to good or even very good ability to predict one of the above events taking place either on the day of the test or during the following calendar day (imminent event).

Methods

This study of laboratory data and their link with deaths is part of an ongoing audit of emergency activity and mortality approved by the Austin Hospital Human Research Ethics Committee, which waived the need for informed consent for this specific project. Data from the period 1 January 2000 to 30 June 2006 were obtained.

Information about the date of all MET calls, ICU admissions and deaths at the Austin Hospital, Melbourne, Australia was collected in specific dedicated electronic databases. These databases were used to identify the patients who received a MET call, were admitted to ICU or died and the date of their death. The central laboratory of our hospital electronically stores all laboratory results with time and date of test. This information can be linked to each patient by means of an individual medical record number and related to the outcome databases.

Data preparation

We obtained data on 30 common laboratory measurements (Item 1, Appendix S1). Laboratory results were provided in batches, where each batch represented some subset of the 30 variables for a patient. Examples of batches include ‘Na, K, Cl, U, cr, total bicarbonate, Hb, Hct, WCC, Plat’ or ‘Na, K, Cl, U, cr, total bicarbonate, Bili, ALP, ALT, GGT, ALB’.

Each laboratory batch taken from an ED patient has an associated batch result time, with date and time of receipt by the laboratory. If the patient had a MET call within 24 h of the batch receipt, or if the patient was admitted to ICU on the same or following day, or the patient died on the same or following day of the batch receipt, the batch was labelled ‘MET’ or ‘ICU’ or ‘DEATH’, respectively; otherwise, it was labelled ‘non-MET’, ‘non-ICU’ or ‘non-DEATH’. Thus, for each batch, we could determine where the patient was and whether a MET or ICU admission or death occurred imminently. We then linked the laboratory data for every patient and tested the ability of each variable to predict these three outcomes using both receiver operating characteristic (ROC) curves, their area under the ROC curve (AUC-ROC) and, where useful, a range of other standard predictive measures for specific cut-off thresholds (sensitivity, specificity, positive predictive value, negative predictive value and diagnostic odds ratio).

Statistical analysis

We initially randomly chose 7000 patients and all their associated test batches (15 092 batches in total) for use in deciding which of the 30 laboratory variables were most promising for further investigation. For each
laboratory variable in these 15,092 batches, we used it as an independent variable for building a univariate logistic regression model (dependent variable of DEATH vs non-DEATH) and computed a P-value assessing the significance of its coefficient using the Wald test. We chose the top nine most statistically significant variables for further investigation. We limited our study to these nine variables to achieve a balance between analysis complexity and clinical utility. The 15,092 batches of tests used in this variable selection step were not subsequently used in the study, to avoid bias. For each of the nine selected variables, we computed standard errors or interquartile ranges. To account for the fact that some patients received multiple tests of a given laboratory variable, a clustered bootstrap technique was used to compute standard errors and interquartile ranges (Item 2, Appendix S1). When reporting the P-variable for each variable obtained from univariate logistic regression as above, to account for multiple hypothesis testing (48 hypotheses: 30 for the death outcome, nine for ICU admission and nine for MET call), Bonferroni correction was applied to the P-values obtained.

**Statistical power considerations**

For each of the nine laboratory variables, we computed a P-value assessing its significance for predicting the outcome using a univariate logistic regression model (as described above). We also assessed the statistical power here for a range of scenarios, using a two-tailed z-test with alpha of 0.001 (= 0.05/48, due to Bonferroni correction).

The scenarios covered varying odds ratio (1.1, 1.2, 1.3, 1.4) and varying sample size.

Sample sizes of approximately 70,000–80,000 were typical for albumin and bilirubin and sample sizes of approximately 130,000 were typical for haemoglobin, haematocrit, total bicarbonate, white cell count, creatinine and urea.

**Predictive value**

We assessed the AUC-ROC to estimate the predictive value of each variable.

We evaluated the AUC-ROC for each of the nine variables for MET call, ICU or death occurring on the same or following day. We also evaluated the metrics of sensitivity, specificity, positive predictive value, negative predictive value and diagnostic odds ratio for a range of cut-off thresholds.

We also used multivariate logistic regression to further investigate the predictive power of the variables in combination (Item 2, Appendix S1). As the outcomes of MET, death and ICU admission were rare in comparison with non-MET, non-death and non-ICU admission, we evaluated whether the use of a statistical correction for rare events in logistic regression would be desirable. The AUC-ROCs when using the rare events logistic regression were virtually identical to the AUC-ROC when using regular logistic regression. We therefore report our results using regular logistic regression.

Goodness-of-fit statistics were computed for the multivariate models using the Hosmer–Lemeshow method (HL c statistic), based on deciles. The P-value associated with this statistic was considered significant at the 0.05 level.

We defined an AUC-ROC as poor if its value was <0.7, fair if its value was >0.7 but <0.80, good if its value was >0.80 but <0.90 and outstanding if its value was >0.90.

Finally, in a further assessment of the external validity of the model developed at the Austin Hospital, we tested it on a separate large cohort of patients admitted to the ED in another tertiary hospital in the city of Melbourne (Alfred Hospital).

**Results**

Having selected nine chosen variables, we studied their values across 160,341 batches of tests in 71,453 ED patients (male: 50.5%; average age: 59.9 ± 22.1 years) for a total of >2.5 million individual measurements and >1 million individual measurements of the nine key variables. Patient population characteristics are summarised in Item 6 of Appendix S1.

Among study patients, 341 had at least one MET call with 557 batches of laboratory tests taken in the 24 h before the call. There were 160 patients with at least one ICU admission with 456 batches of tests taken on the day before or the day of ICU admission and there were 858 patients who died with 1760 batches taken on the day before or the day of death.

The significance of each laboratory variable to predict a MET call within 24 h was also assessed and found to be significant for nearly all variables (shown in Table 1). The mean and median of each variable
measured during the 24 h before a MET call, or during other periods, were also calculated and are shown in Table 1. Such other period might have occurred before or after the event and might have been influenced by treatment. These differences were similar for ‘ICU admission’ versus ‘non-ICU admission’ and even more significant for ‘Death’ versus ‘non-Death’ (see Tables 3 and 4 in Item 3, Appendix S1). Calculations of statistical power are shown for a range of scenarios in Appendix S1 Item 5. The highest power exists for detecting effects for the death outcome, followed by the MET outcome and then the ICU outcome. These figures are in accordance with the relative proportion of cases for each outcome.

The estimated predictive ability of each key laboratory variable is shown in Table 2. This table shows that some individual laboratory variables had good predictive value for imminent MET call, ICU admission or death. Importantly, predictive laboratory test results were, on average, available 11.9 h before a MET call was made.

Construction of logistic models used 75 195 batches. For the prediction of a MET call, the logistic model had an AUC-ROC of 0.69 (95% CI 0.63–0.74; HL-statistic 5.4); for the prediction of ICU admission, the model's AUC-ROC was 0.82 (95% CI 0.73–0.87; HL-statistic 18.2); for the prediction of death, the model’s AUC-ROC was 0.90 (95% CI 0.87–0.91; HL-statistic 6.2) (Fig. 1).

The logistic regression model formulae for all models are presented in detail in Appendix S1 (Items 4A, 4B and 4C). Models were well calibrated despite testing on very large cohorts, which biases the HL-statistic towards lower P-values (see Appendix S1 Items 4A, 4B and 4C). The AUC-ROC ranged from good to excellent. From the ROC curves, by choosing appropriate cut-off thresholds, values for sensitivity and specificity could be derived (see Appendix S1 Items 4A, 4B and 4C). For each decision cut-off, these tables also show the batch having the lowest risk score out of all the results for which the outcome is predicted to occur.

In the external validation cohort, we studied 37 367 batches collected from 21 430 patients during 2011 at the Alfred Hospital. There were 162 deaths, 56 ICU admissions and 255 MET calls. Testing of the logistic multivariate model used 21 327 batches with 143 labelled death, 51 labelled ICU and 191 labelled MET. In these patients, the multivariate model’s AUC-ROC for imminent death was 0.89 (95% CI 0.86–0.91; HL-statistic

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### Table 1. Comparison of nine key laboratory variables for patients who did or did not have a medical emergency team (MET) call

<table>
<thead>
<tr>
<th>Variable</th>
<th>MET</th>
<th>Non-MET</th>
<th>P-value (corrected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/L)</td>
<td>125 ± 24.4</td>
<td>133 ± 20.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td># tests (# patients)</td>
<td>355 (322)</td>
<td>133 082 (70 659)</td>
<td></td>
</tr>
<tr>
<td>Haematocrit (L/L)</td>
<td>0.377 ± 0.071</td>
<td>0.396 ± 0.0568</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td># tests (# patients)</td>
<td>355 (322)</td>
<td>133 015 (70 647)</td>
<td></td>
</tr>
<tr>
<td>Total bicarbonate (mmol/L)</td>
<td>23.9 ± 5.09</td>
<td>24.7 ± 3.63</td>
<td>0.002</td>
</tr>
<tr>
<td># tests (# patients)</td>
<td>360 (324)</td>
<td>129 716 (66 415)</td>
<td></td>
</tr>
<tr>
<td>White cell count (10⁹/L)</td>
<td>10.2 (7.82, 14.5)</td>
<td>8.5 (6.7, 11.2)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Median (IQ range)</td>
<td>355 (322)</td>
<td>133 012 (70 650)</td>
<td></td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>33.6 ± 6.4</td>
<td>37.1 ± 5.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td># tests (# patients)</td>
<td>266 (248)</td>
<td>85 631 (49 545)</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.34 ± 0.0662</td>
<td>7.38 ± 0.106</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td># tests (# patients)</td>
<td>222 (131)</td>
<td>26 683 (12 566)</td>
<td></td>
</tr>
<tr>
<td>Bilirubin (µmol/L)</td>
<td>14 (9.0, 21.8)</td>
<td>11 (8, 17)</td>
<td>0.32</td>
</tr>
<tr>
<td>Median (IQ range)</td>
<td>247 (236)</td>
<td>78 088 (46 777)</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mmol/L)</td>
<td>0.104 (0.078, 0.164)</td>
<td>0.082 (0.066, 0.106)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td># tests (# patients)</td>
<td>361 (324)</td>
<td>129 759 (66 431)</td>
<td></td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>9.2 (5.77, 15.40)</td>
<td>6 (4.4, 8.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td># tests (# patients)</td>
<td>361 (324)</td>
<td>129 733 (66 419)</td>
<td></td>
</tr>
</tbody>
</table>

Hb, haemoglobin concentration (g/L); Hct, haematocrit concentration (L/L); Total bicarbonate, bicarbonate + carbonic acid; WCC, white cell count (×10⁹/L); ALB, albumin concentration (g/L); Bili, bilirubin (µmol/L); U, urea (mmol/L); cr, creatinine (mmol/L); pH. Mean/median values and standard deviation (SD)/interquartile (IQ) ranges, as well as number of tests (number of patients), for each variable shown for group labelled with the MET event and group labelled with the non-MET event, with P-values assessing the significance of the variable for predicting MET call, corrected for multiple testing. Tests refers to the number of tests performed and patients to the number of patients generating the tests. The much smaller number of tests in the non-survivors is due to the fact that tests assessed relate only to the 24 h before the event.
Table 2. Predictive ability of single biochemical variables for the three key study outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>MET call AUC-ROC [95% CI]</th>
<th>ICU admission AUC-ROC [95% CI]</th>
<th>Death AUC-ROC [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin</td>
<td>0.610 [0.580–0.643]</td>
<td>0.5845 [0.5387–0.6299]</td>
<td>0.6330 [0.6133–0.6532]</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>0.587 [0.557–0.621]</td>
<td>0.5489 [0.4996–0.5993]</td>
<td>0.5788 [0.5562–0.6004]</td>
</tr>
<tr>
<td>Total bicarbonate</td>
<td>0.557 [0.527–0.593]</td>
<td><strong>0.7820 [0.7439–0.8212]</strong></td>
<td>0.7318 [0.7126–0.7515]</td>
</tr>
<tr>
<td>WCC</td>
<td>0.625 [0.595–0.657]</td>
<td>0.6304 [0.5838–0.6750]</td>
<td>0.6913 [0.6711–0.7099]</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.660 [0.626–0.693]</td>
<td><strong>0.7244 [0.6775–0.7683]</strong></td>
<td>0.7791 [0.7614–0.7966]</td>
</tr>
<tr>
<td>pH</td>
<td>0.631 [0.595–0.669]</td>
<td><strong>0.7926 [0.7659–0.8170]</strong></td>
<td>0.8069 [0.7913–0.8211]</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>0.580 [0.543–0.618]</td>
<td>0.5661 [0.5161–0.6147]</td>
<td>0.5799 [0.5574–0.6020]</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.655 [0.624–0.685]</td>
<td><strong>0.7461 [0.7116–0.7840]</strong></td>
<td>0.7645 [0.7494–0.7803]</td>
</tr>
<tr>
<td>Urea</td>
<td>0.674 [0.644–0.705]</td>
<td>0.6976 [0.6565–0.7369]</td>
<td>0.7905 [0.7766–0.8059]</td>
</tr>
</tbody>
</table>

Hb, haemoglobin concentration (g/L); Hct, haematocrit concentration (L/L); Total bicarbonate, bicarbonate + carbonic acid (mmol/L); ALB, albumin (g/L); Bili, bilirubin (µmol/L); WCC, white cell count (×10⁹/L); cr, creatinine (mmol/L); U, urea (mmol/L). Values >0.70 highlighted in bold. AUC-ROC, area under the receiver operating characteristic curve; ICU, intensive care unit; MET, medical emergency team.

Figure 1. ROC curve for a logistic model using key laboratory variables for the prediction of imminent death. AUC-ROC = 0.872. AUC-ROC, area under the receiver operating characteristic curve.

4.1); for ICU admission it was 0.84 (95% CI 0.78–0.90; HL-statistic 15.3); for MET call it was 0.70 (95% CI 0.66–0.73; HL-statistic 33.3).

Discussion

Statement of key findings

We studied more than 70,000 ED patients to test whether commonly measured laboratory variables predict imminent (occurring on the same or following day) MET calls, unplanned ICU admission or death. We found that several combinations of tests had fair, good, very good or even excellent predictive values. We further found that combinations of tests and specific thresholds could define potentially clinically useful levels of specificity and/or sensitivity for such prediction to inform operational rules to identify such patients. Finally, using data from a separate teaching hospital ED, we externally validated the performance robustness of these models.

Comparison with previous studies

To our knowledge, this is the first comprehensive assessment of multiple commonly measured laboratory tests as predictors of imminent key adverse events in a heterogeneous group of ED patients. However, the use of some laboratory tests to predict mortality is well described for specific conditions and groups of patients.22-25,29-32 In addition, the use of laboratory tests in conjunction with vital signs is well established in the critical care literature to generate illness severity scores and predict outcome.19,20 By analogy, common laboratory tests might also prove useful in identifying patients at risk within the ED. However, so far, investigators have mostly focused on vital signs to achieve early identification of patients at risk18,26 with AUC-ROC values between 0.65 and 0.85.5 When attempts have been made to develop predictive models for ED patients,2,4 they have been disease- or condition-specific,13-18 have used ICU-developed illness severity scores,4 selected physiological abnormalities assessed with vital sign acquisition2,4 When general studies have been performed in ED...
patients or patients just admitted to hospital, they either have used clinical data to improve their predictive capability, have not considered ED patients separately, or have not developed a predictive model. Ours is therefore the first study that identifies a method to detect any ED patients not just at significant risk of major adverse events sometime during their hospital stay but rather at risk of an imminent event, a physiological state of clear and present danger.

**Clinical implications**

This study provides evidence that commonly measured laboratory tests can help identify ED patients at risk of an imminent adverse event. Although the appreciation that abnormal laboratory tests are associated with greater risk is intuitive, outside of statistical modelling it is impossible for clinicians to quantify such risk. The clinical implications of such discrimination and diagnostic specificity are obvious.

Some combinations of abnormalities that identify extremely high-risk patients are not always clinically intuitive and our methodology can uncover unappreciated patterns. Such discovery has the potential to help physicians learn what patterns identify unstable physiology in different age groups early in their development. The ability to identify at-risk patients early is logical because most have antecedent abnormalities before adverse events and important because non-identification or delayed identification is associated with increased mortality. Accordingly, our study implies that commonly collected, electronically available laboratory information can be incorporated into an early warning system. Similar alert systems with prompts for the use of medications have been proven effective in decreasing morbidity, and automated clinical alerts based on vital signs have reported a decrease in length of hospital stay.

**Strengths and limitations of the study**

This study has several strengths. It involves more than 70,000 patients and 2.5 million single tests in the development cohort. It is the first study of this kind in ED patients. Within this large cohort, we found good predictive ability despite the low prevalence of the target events. In the case of MET calls, identification was possible on average approximately 12 h before each event, allowing sufficient time for intervention. This is a single-centre study and its findings might not apply to patients in other hospitals. However, our hospital has all the typical performance characteristics of other tertiary institutions, thus carrying a likelihood of external validity within our country, and such external validity was confirmed by the application of the model to a set of data from the ED of another Australian teaching hospital. Yet, our findings might not apply to other countries or healthcare systems. Fuzzy controller or artificial neural network prediction systems might perform even better. We hope to test them in the near future. Ideally, a laboratory-based system like this should be combined with clinical data. Unfortunately, numerical ED-obtained clinical data have only recently become available in our hospital. No electronically accessible information was available regarding planned versus unplanned ICU admissions and/or limitation of medical therapy. These aspects of ED care are likely to profoundly influence outcome, and our inability to obtain such data limits the robustness of any predictive inferences. Some of the differences we show in the mean value of key variables, although highly significant at a statistical level, might appear of limited clinical relevance. However, this might reflect the limited ability of the human mind to discern the predictive value of more subtle differences. We cannot provide cut-off values for clinical decision making because a given cut-off value might be entirely inappropriate in a particular context (e.g. urea in a patient presenting with a broken leg who is about to undergo his/her dialysis session). Thus, our analysis can only offer a broad population risk estimate for all patients with a particular set of laboratory values. Such population risk assessment can then be incorporated into clinical judgment at the bedside. This is an observational study with all the inherent limitations of such design. Thus, no inferences can be made on the ability of these findings to improve patient care. Prospective randomised controlled studies are needed. However, this study represents the first and necessary step in the design of such trials and might assist, together with new approaches to vital sign charting and ED-based early warning systems, in making EDs safer.

**Conclusions**

In ED patients, we found that combinations of laboratory tests had fair, good or very good predictive value in identifying patients at risk of imminent MET calls, ICU admission or death within the same or next day. These findings provide proof-of-concept evidence that laboratory tests can be used to assist in the early identification of high-risk ED patients.
Acknowledgements

The authors acknowledge the work of Mr Lawrence Hudson and Mr Christopher MacManus of the Health Informatics Department at Alfred Health in assisting with obtaining ethics approval for the project, and with data extraction and management. This project was partially supported by the Cooperative Research Centres Programme for Smart Services funded by the Australian Government.

Author contributions

RB, GKH, EL and JB conceived the study. CH, PD, CB, DP and HS helped obtain the relevant data. EL and JB conducted the statistical analysis. EL, RB and JB developed the first draft of the manuscript. All authors contributed to the final draft.

Competing interests

None declared.

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References


**Supporting Information**

Additional Supporting information may be found in the online version of this article:

**Appendix S1.** Detailed description of study variables and statistical calculations and methodology.