Clinical paper

Common laboratory tests predict imminent death in ward patients

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ARTICLE INFO

ABSTRACT

Objective: To estimate the ability of commonly measured laboratory variables to predict an imminent (within the same or next calendar day) death in ward patients.
Design: Retrospective observational study.
Setting: Two university affiliated hospitals.
Patients: Cohort of 42,701 patients admitted for more than 24 hours and external validation cohort of 13,137 patients admitted for more than 24 hours.
Intervention: We linked commonly measured laboratory tests with event databases and assessed the ability of each laboratory variable or combination of variables together with patient age to predict imminent death.
Measurements and main results: In the inception teaching hospital, we studied 418,897 batches of tests in 42,701 patients (males 55%; average age 65.8 ± 17.6 years), for a total of >2.5 million individual measurements. Among these patients, there were 1596 deaths. Multivariable logistic modelling achieved an AUC–ROC of 0.87 (95% CI: 0.85–0.89) for the prediction of imminent death. Using an additional 105,074 batches from a cohort of 13,137 patients from a second teaching hospital, the multivariate model achieved an AUC–ROC of 0.88 (95% CI: 0.85–0.90).
Conclusions: Commonly performed laboratory tests can help predict imminent death in ward patients. Prospective investigations of the clinical utility of such predictions appear justified.

1. Introduction

Among hospital patients, serious adverse events, including death, are relatively common.[1–3] Many such events and deaths appear preventable[1–6] because they are preceded by physiological and clinical deterioration. Multiple attempts have been made to avoid such deaths[5–10] including the introduction of rapid response teams (RRTs) systems to respond to acute physiological deterioration.[9] Such systems, however, are problematic because the identification of patients at risk is subject to the accuracy of observations,[9] judgment about the patient's condition,[8] diligence in the measurements of vital signs,[8–11] vigilance during the entire 24 hour period,[11] and, finally, willingness to call for help in a timely fashion.[12–15] These shortcomings contribute to incorrect non-activation or delayed activation of an appropriate response to patient deterioration.[14–16] Non-activation and delayed activation are, in turn, associated with increased mortality.[14,15,17,18] These recurrent observations suggest the need for a better approach so that an appropriate response can occur, or where necessary, earlier end of life discussion can take place and unnecessary and unwanted chest compression can be avoided.

A system based on objective data electronically collected as part of standard care might assist in the identification of high risk patients. Such data already exist in essentially all hospitals of developed countries in the form of common laboratory tests (e.g. biochemistry, hematology, arterial blood gases). In association with clinical information, they have already been found helpful in estimating risk of the death after ICU admission[19,20] and in cohorts of ward patients.[21,22] It seems, therefore, physiologically plausible and, by analogy, logical, that laboratory data might similarly help identify other hospital patients at risk of imminent death.

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Accordingly, we performed a study to determine whether common laboratory variables might serve as useful predictors of imminent death in ward patients. In particular, we hypothesised that commonly performed laboratory tests, when used in combination, might have a fair to good ability to predict the patient's death either on the same day or during the following calendar day (imminent death).

2. Methods

This study of laboratory data and their link with deaths is part of a continuing audit of emergency activity and mortality approved by the Austin and Alfred Hospital Human Research Ethics Committees, which waived the need for informed consent for this specific project.

Information about the date of all deaths at the Austin and Alfred Hospital is collected in a specific dedicated administrative electronic database. Similarly, the central laboratory of the hospitals electronically stores all laboratory results with time and date of test. The information from these databases can be linked to each patient by means of an individual medical record number. We did not exclude patients with do not attempt resuscitation (DNAR) orders from analysis.

2.1. Data preparation

We obtained data on 30 common laboratory measurements. Laboratory results were provided in batches, where each batch represents 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 a ward patient has an associated batch result time. This time and date were those of receipt and time stamping by the laboratory.

If the patient died on the day of the batch receipt or on the day following the batch receipt, the batch of tests was labelled "DEATH"; otherwise it was labelled "non-DEATH".

For each batch, we could determine where the patient was and whether death occurred on the same or following day of receipt by the laboratory. We labelled a death occurring with the same or next day of such receipt as imminent death.

We then linked the laboratory data for every patient and tested the ability of each variable to predict death 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).

2.2. Statistical analysis

We initially randomly chose 3000 patients and all their associated test batches (40,062 batches in total) for use in deciding which of the 30 variables were most promising for further investigation. For each variable in these 40,062 batches, we compared its measurements from batches labelled DEATH against its measurements from batches labelled non-DEATH, using a t-test for parametric data or the Mann–Whitney U test for non-parametric data. To account for multiple hypothesis testing (30 hypotheses), Bonferroni correction was applied to the p-values obtained. To account for the fact that some patients received multiple tests of a given lab variable, a clustered bootstrap technique was used to compute standard errors and interquartile ranges. 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 40,062 batches of tests used in this

variable selection step were not subsequently used in the study, to avoid bias.

2.3. Predictive value

We assessed the area under the receiver operating characteristic curve (AUC–ROC) to estimate the predictive value of each variable or combination of variables together with patient age to predict imminent death.

We evaluated the area under the AUC–ROC for each of the nine variables for DEATH occurring on the same or following day. We also evaluated the metrics of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive (LR+) and negative likelihood (LR−) ratios and diagnostic odds ratio (DOR) for a range of cut-off thresholds.

We used multivariate logistic regression to further investigate the predictive power of the variables in combination. Since the DEATH outcome was rare in comparison to non-DEATH, we evaluated whether the use of a statistical correction for rare events in logistic regression would be desirable.[23] The AUC–ROC when using the rare events logistic regression was virtually identical to the AUC–ROC when using regular logistic regression. We therefore report our results just for regular logistic regression. We calculated confidence intervals for the logistic regression model performance statistics, using a clustered bootstrap methodology.

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.

Goodness of fit statistics were computed for the multivariate models using the Hosmer–Lemeshow method (H–L GOF statistic), based on deciles. The p-value associated with this statistic was considered significant at the 0.05 level.[24] Thus, if a model had an associated p-value > 0.05, then the null hypothesis of goodness of fit was not rejected.

Finally, in a further assessment of the external validity of the model developed at the Austin Hospital, we tested it a separate cohort of patients form another teaching hospital in the city of Melbourne (Alfred Hospital)

3. Results

Having selected nine chosen variables, we studied their values across 418,897 batches of tests in 42,701 ward patients (males: 55%; average age: 65.8 ± 17.6 years) for a total of >2.5 million individual measurements.

Among study patients, there were 1596 patients who died with 3064 batches taken on the day prior to or the day of death. The test results measured during the day of or the day before a death were compared with the same test results measured during other periods as shown in Table 1 and found to be significantly different ($p < 0.0001$) for all variables.

The estimated predictive ability of each key laboratory variable is shown in Table 2. This table shows that some individual laboratory variables had fair predictive value for imminent death.

Construction of logistic multivariate models used 118,999 batches, with 808 labelled DEATH. For the prediction of imminent death the model's AUC–ROC was 0.87 (95% CI: 0.85–0.89; HL-statistic: 13.6) (Fig. 1). As an example, the prediction performance for the multivariable logistic model across varying decision cut-offs for death and the logistic regression formula for the prediction of imminent death are presented in Table 3. For each decision cut-off, this table also shows the batch having the lowest risk score out of all the results for which death is predicted to occur. From these curves, by choosing appropriate cut-off thresholds, values for sensitivity and specificity could be derived.

Table 1
Comparison of nine key laboratory variables for patients who did or did not die.

	Died	Survived	*p*-Value (corrected)
Hb			
Mean ± s.d.	106.6 ± 22.5	110.8 ± 20.1	<0.0001
Tests	2106	350,103	
Patients	1434	41,071	
Hct			
Mean ± s.d.	0.33 ± 0.07	0.34 ± 0.06	<0.0001
Tests	2096	348,605	
Patients	1431	40,959	
Total bicarbonate			
Mean ± s.d.	22.8 ± 7.2	25.7 ± 4.3	<0.0001
Tests	2283	368,082	
Patients	1500	40,767	
WCC			
Median (IQ range)	12.3 (8.4, 17.6)	8.2 (6.1, 10.8)	<0.0001
Tests	2098	348,315	
Patients	1431	40,959	
ALB			
Mean ± s.d.	24.4 ± 7.2	28.5 ± 6.6	<0.0001
Tests	1147	163,896	
Patients	874	28,398	
pH			
Mean ± s.d.	7.28 ± 0.15	7.39 ± 0.10	<0.0001
Tests	649	17,175	
Patients	437	6681	
Bili			
Median (IQ range)	18 (11, 40)	13 (8, 23)	<0.0001
Tests	853	127,237	
Patients	685	25,858	
cr			
Median (IQ range)	0.15 (0.09, 0.24)	0.09 (0.07, 0.13)	<0.0001
Tests	2286	368,220	
Patients	1503	40,777	
U			
Median (IQ range)	15.8 (9.3, 24.2)	6.7 (4.3, 11.2)	<0.0001
Tests	2284	368,176	
Patients	1502	40,770	

Hb: hemoglobin concentration (g/L); Hct: hematocrit concentration (L/L); total bicarbonate: bicarbonate + carbonic acid; WCC: white cell count ($\times 10^9$/L); ALB: albumin concentration (g/L); Bili: bilirubin (μmol/L); U: urea (mmol/L); cr: creatinine (mmol/L) and pH. Mean/median values and standard deviation/interquartile ranges, as well as number of tests (number of patients), for each variable shown for group labelled with the DEATH event and group labelled with the non-DEATH event, with *p*-values assessing the significance of the distribution difference between the groups, corrected for multiple testing. The term "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 day of and the day before the event.

Table 2
Predictive ability of single biochemical variables for predicting death.

Variable	Death AUC–ROC (95% CI)
Hb	0.5582 (0.5456, 0.5706)
Hct	0.5303 (0.5181, 0.5427)
Total bicarbonate	0.6506 (0.6358, 0.6632)
WCC	0.7063 (0.6932, 0.7189)
ALB	0.6628 (0.6472, 0.6801)
pH	0.7254 (0.7035, 0.7490)
Bili	0.6131 (0.5945, 0.6317)
cr	0.6870 (0.6767, 0.6972)
U	0.7724 (0.7625, 0.7818)

Hb: hemoglobin concentration (g/L); Hct: hematocrit concentration (L/L); total bicarbonate: bicarbonate + carbonic acid; WCC: white cell count ($\times 10^9$/L); ALB: albumin concentration (g/L); Bili: bilirubin (μmol/L); U: urea (mmol/L); cr: creatinine (mmol/L) and pH.
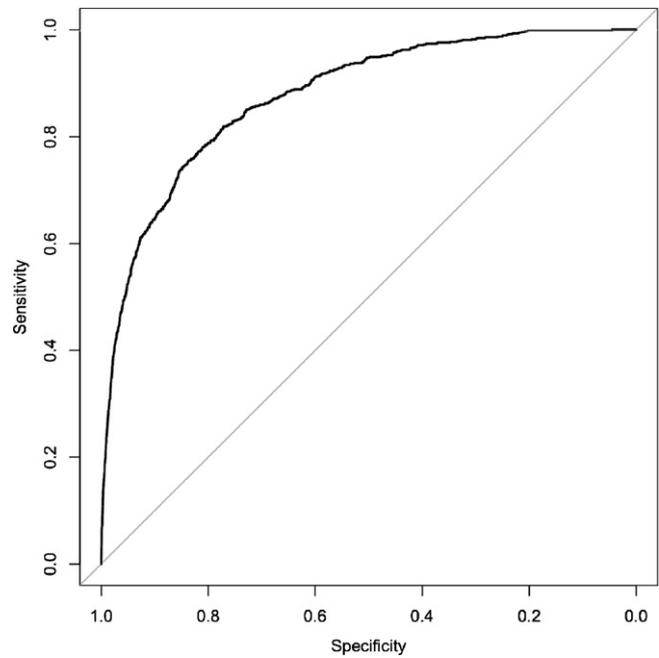

Fig. 1. ROC curve for a logistic model using key laboratory variables for the prediction of imminent death. AUC–ROC = 0.872.

In the external validation cohort from a second teaching hospital, we studied 105,074 batches collected from 13,137 patients during 2011. There were 702 deaths. Testing of the logistic multivariate model used 39,066 batches with 195 labelled death. In these patients, the multivariate model's AUC–ROC for imminent death was 0.88 (95% CI: 0.85–0.90; HL-statistic: 16.1).

4. Discussion

4.1. Statement of key findings

We conducted a study of more than 40,000 ward patients from a tertiary hospital admitted for >24 hours to test whether commonly measured laboratory variables would help predict imminent death. We found combinations of such tests had fair to good predictive values. We further found that, using combinations of tests and specific thresholds, we could define potentially clinically useful levels of specificity and/or sensitivity for such predictions. Finally, we confirmed the potential external validity of our findings by applying our predictive model to another large cohort of patients from another teaching hospital.

4.2. Comparison with previous studies

To the best of our knowledge, this is the first comprehensive assessment of multiple commonly measured laboratory tests as predictors of imminent death in ward patients. However, the use of some laboratory tests to predict mortality is established in the medical literature for specific conditions and groups of patients.[25,26] In addition, the use of laboratory tests in conjunction with clinical assessment of vital signs is well established in the critical care literature to generate illness severity scores and predict outcome.[19,20] Finally, as is the case with physiological variables,[27,28] the combination of multiple laboratory tests to develop predictive models has been investigated in a number of previous studies dealing with general ward patients, surgical patients or emergency department patients.[28–37] In all such studies, predictive models based on laboratory measurements have been found to achieve fair to good discrimination. In addition, investigators have focused on vital

Table 3
Prediction performance for multivariate model across varying decision cut-off values for death. An example batch of results at each risk score decision cut-off is shown in the first column.

Risk score (Age, U, cr, CO2, Bili, ALB, Hb, Hct, WCC)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	DOR (95%CI)
≥0.0078295 (90, 11.3, 0.156, 21, 40, 32, 127, 0.38, 11.2)	0.755 (0.724 0.784)	0.837 (0.835 0.840)	0.0307 (0.0284 0.0332)	0.998 (0.998 0.998)	15.8 (13.5 18.6)
≥0.0185 (64, 20.5, 0.101, 21, 320, 22, 124, 0.35, 13.2)	0.574 (0.539 0.609)	0.936 (0.935 0.937)	0.0578 (0.0528 0.0631)	0.997 (0.997 0.997)	19.7 (17.1 22.7)
≥0.0385 (66, 26.2, 0.243, 13, 21, 18, 87, 0.27, 6.2)	0.405 (0.371 0.439)	0.975 (0.974 0.976)	0.100 (0.090 0.111)	0.996 (0.995 0.996)	26.7 (23.1 30.8)
≥0.0585 (86, 33.5, 0.307, 15, 87, 40, 87, 0.28, 10)	0.291 (0.260 0.323)	0.986 (0.986 0.987)	0.126 (0.111 0.142)	0.995 (0.995 0.995)	29.3 (25.0 34.3)
≥0.0785 (73, 13.8, 0.137, 18, 11, 16, 71, 0.23, 16.2)	0.228 (0.199 0.258)	0.990 (0.990 0.991)	0.144 (0.125 0.164)	0.995 (0.994 0.995)	31.6 (26.5 37.6)
≥0.13 (83, 31.3, 0.478, 11, 27, 7, 61, 0.17, 11.3)	0.149 (0.125 0.175)	0.996 (0.995 0.996)	0.194 (0.164 0.228)	0.994 (0.994 0.995)	41.3 (33.4 51.1)

Values shown for sensitivity, specificity, positive prediction value (PPV), negative predictive value (NPV) and diagnostic odds ratio (DOR). Bold value indicates the threshold maximising value of sensitivity + specificity.

Logistic regression formula: Score = $0.0332 \times$ Age + $0.0657 \times$ U − $1.3231 \times$ cr + $2.6791 \times CO2\_1$ + $1.5819 \times CO2\_2$ + $1.105 \times CO2\_3$ + $0.874 \times CO2\_4$ + $0.4341 \times CO2\_5$ + $0.1303 \times CO2\_6$ − $0.4348 \times CO2\_7$ − $0.1534 \times CO2\_8$ + $0.5027 \times CO2\_9$ + $0.002 \times$ Bili − $0.0589 \times$ ALB − $0.081 \times$ Hb + $28.8029 \times$ Hct + $2.5632 \times WCC\_1$ − $0.5169 \times WCC\_2$ − $0.1731 \times WCC\_3$ + $0.3902 \times WCC\_4$ + $0.6851 \times WCC\_5$ + $1.2734 \times WCC\_6$ − 7.1811
where age: age (years); Hb: hemoglobin concentration (g/L); Hct: hematocrit concentration (L/L); CO2: total bicarbonate concentration (mmol/L); WCC: white cell count ($\times 10^9$/L); ALB: albumin concentration (g/L); Bili: bilirubin (μmol/L); U: urea (mmol/L); cr: creatinine (mmol/L)
and
$CO2\_1 = 1$ if $CO2 \in$ (−inf to 9.5) and 0 otherwise,
$CO2\_2 = 1$ if $CO2 \in$ (9.5–13.5) and 0 otherwise,
$CO2\_3 = 1$ if $CO2 \in$ (13.5–16.5) and 0 otherwise,
$CO2\_4 = 1$ if $CO2 \in$ (16.5–18.5) and 0 otherwise,
$CO2\_5 = 1$ if $CO2 \in$ (18.5–19.5) and 0 otherwise,
$CO2\_6 = 1$ if $CO2 \in$ (19.5–22.5) and 0 otherwise,
$CO2\_7 = 1$ if $CO2 \in$ (22.5–32.5) and 0 otherwise,
$CO2\_8 = 1$ if $CO2 \in$ (32.5–36.5) and 0 otherwise,
$CO2\_9 = 1$ if $CO2 \in$ (36.5–inf) and 0 otherwise,
$WCC\_1 = 1$ if $WCC \in$ (−inf to 0.25) and 0 otherwise,
$WCC\_2 = 1$ if $WCC \in$ (0.25–9.65) and 0 otherwise,
$WCC\_3 = 1$ if $WCC \in$ (9.65–12.45) and 0 otherwise,
$WCC\_4 = 1$ if $WCC \in$ (12.45–14.05) and 0 otherwise,
$WCC\_5 = 1$ if $WCC \in$ (14.05–17.35) and 0 otherwise,
$WCC\_6 = 1$ if $WCC \in$ (17.35–inf) and 0 otherwise.

signs, often combined into scoring systems to achieve the early identification of patients at risk with predictive values similar to those found in our using laboratory models.[38–40] Given the above large body of previous research in the field of risk stratification, we reasoned that common laboratory tests might also prove useful in identifying patients at risk of imminent death.

4.3. Clinical implications

This study provides evidence that commonly measured laboratory tests can help identify ward patients at risk of imminent death with a predictive ability similar or superior to emerging diagnostic biomarkers for other conditions[41–46] and similar to that reported for vital sign-based early warning scores.[38–40]

Although the appreciation that abnormal laboratory tests are associated with greater risk is intuitive, outside of statistical modelling, it is impossible for clinicians to allocate a quantitative and/or predictive value to imminent risk. The clinical implications of having such knowledge, discrimination and diagnostic assistance can be intuitively understood.

Beyond the above considerations, some combinations of abnormalities, which identify those patients at risk of imminent death, are not always clinically intuitive. Thus, our methodology can uncover patterns that are not easily quantifiable by the experienced clinicians. Such discovery has the potential to help physicians learn what patterns of tests identify imminent risk in different age groups early in their development. The ability to identify at imminent risk patients as early as possible is logical because most have antecedent abnormalities before adverse events.[47,48] It is also important because, in many of these patients, non-identification or delayed identification are associated with non-intervention or delayed intervention,[15,16] inferior documentation of end-of-life care wishes[49] and increased mortality.[15,16] Conversely, early intervention and preventive activity are associated with decreased morbidity and mortality.[18,50,51]

Our study also implies that commonly collected, electronically available laboratory information can be incorporated into an early warning system. For example, this information could be used to activate paging systems within the hospital to alert the relevant clinicians and the RRT and simultaneously quantify likely risk. Such a system, by harnessing electronic information, has the potential to improve hospital medicine. Similar alert systems[52] with prompts for the use of medications have been proven effective in decreasing morbidity and recent studies of automated clinical alerts based on vital signs have reported a decrease in length of hospital stay.[53] Finally, in institutions where vital signs obtained in ward patients are recorded or obtained electronically, laboratory data and vitals observations could be linked to enhance the ability to identify patients at risk.

4.4. Strengths and limitations of the study

This study has several strengths. It involves more than 40,000 patients and >2.5 million single tests. It is the first study to focus on imminent risk encompassing patients from the general wards. Its findings are internally consistent, biologically plausible and confirmed in a validation statistical assessment. They were further found to have a degree of external validity when applied to a large cohort from another academic hospital and are consistent with a previous large body of evidence showing the overall predictive value of combinations of laboratory tests.[28–37] Within this large cohort, we found good predictive ability despite the low prevalence of the target event. Finally, our model predicts imminent events rather than events occurring as some unspecified time in the future. However, this is a study in two tertiary centres with a primary centre for model development and a secondary centre for external validation of the model. Its findings may not apply to patients in non-tertiary hospitals. Yet, the hospitals involved in this study have all the typical performance characteristics of an academic tertiary institution in a developed country[54] within a

strong health care system,[55,56] thus carrying a likelihood of external validity for similar hospitals worldwide. This is a retrospective observational study with all the inherent limitations of such design. Thus, no inferences can yet 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. The time and date of the laboratory results related to receipt of the specimen by the central laboratory and not the time the blood was collected by venepuncture. This approach may have introduced a bias related to transport delays. We were unable to obtain the time of death as only the date was recorded in the electronic database. This made it impossible to relate the concept of imminent death to a stricter 24 hour period after the collection of a given specimen. The calculations used to create laboratory results-based predictive models are complex and cannot be simplified into a score similar to vital signs based early warning scores. This makes clinical application impossible unless appropriate automated software is installed in laboratory servers to electronically calculate such predictive models and transmit information to clinicians. Whether this can be done remains uncertain. Finally, patients identified as being at risk of imminent death by laboratory tests, may already be receiving palliative care. However, in such patients, appreciation that death is imminent may still be of clinical utility by facilitating family explanations and better end of life care.

5. Conclusions

We conducted a study of more than 2.5 million single measurements and more than 400,000 batches of laboratory tests in more than 40,000 hospital ward patients and found that several individual laboratory tests as well as combinations of tests had fair to good predictive value in identifying patients at risk of death within the same or next day. We confirmed these findings in a separate cohort from another teaching hospital. These findings provide proof-of-concept evidence that laboratory tests can be harnessed to assist in the identification of hospital patients at risk of imminent death.

Conflict of interest statement

We further warrant that all authors have read and approved the manuscript and that there are no conflicts of interest in relation to this paper.

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