

The predictive value of leucocyte progression for one-week mortality on acutely admitted medical patients to the emergency department

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Abstract:

Objective: To clarify if leucocyte count progression can predict one-week mortality in unselected medical patients admitted to the emergency department. Additionally, we investigated the importance of leucocyte count progression for admission to the intensive care unit and length of stay.

Method: This retrospective cohort study uses data collected in two phases from patients admitted through the emergency department at Hospital of South West Jutland. Upon admission, a nurse recorded the primary complaint and vital signs and registered these along with demographic information. Blood test results were subsequently extracted from the hospital's computer systems. Patients were separated into three groups according to the development in their leucocyte count from the day of admission to the day after.

Results: The total cohort was 5894 patients; 30.5% remained after exclusion. Median age was 71, and 50.3% were female. Using logistic regression, we found significantly lower one-week mortality with falling leucocyte count progression, even when controlling for confounders.

A decreasing leucocyte count had a sensitivity for one-week mortality of 65%, specificity of 62%, positive predictive value of 4%, and negative predictive value of 99%.

Difference in admission to the intensive care unit was non-significant between the three groups. Difference in length of stay was significant, but with one day difference, the clinical significance is questionable.

Conclusion: Leucocyte count progression is not sensitive enough to predict one-week mortality, nor specific enough to discount it. It is important for physicians to be aware of this to avoid faulty assessments based on imprecise assumptions.

Introduction

The leucocyte count (LC) is widely used in clinical practice.¹ If the LC decreases after treatment is started, healthcare professionals assume the treatment is working and continue. A decreasing LC could therefore perhaps be considered a good prognostic sign. We have not been able to identify any research that examines LC progression over time, even though the progression of the count is what we build our clinical assessment on. Could a decreasing LC be a sign of leucocytes becoming necrotic and apoptotic, faster than they can be produced? And therefore predict a poor outcome instead of better prognosis? This might be the case with septic patients, who experience massive apoptosis of immune effector cells, which inhibits their ability to eradicate the primary infection.²

By grouping emergency department (ED) patients according to their leucocyte count progression (LCP), we can study whether their prognosis is different, and in accordance with our previous assumptions. With this knowledge, we can decide which patients need extra attention.

The objectives of this study is to clarify if LCP can predict one-week mortality in unselected medical

patients admitted to the ED. Additionally we will investigate the importance of the LCP for admission to the intensive care unit (ICU) and length of stay (LOS).

Method

Study design and data

This retrospective cohort study uses data collected from patients admitted through the ED at Hospital of South West Jutland in two phases. The first period from October 2008 to February 2009 and the second from February 2010 to May 2010. The data was originally collected for another study including all acutely admitted medical patients to the ED. Upon admission, a nurse recorded the primary complaint and the vital signs and registered these along with demographic information. Blood test results were extracted from the hospital's computer systems. No extra biochemical analyses were ordered as part of the study, only analyses ordered by the admitting doctor were included. If a patient had multiple analyses of the same biochemical component, only the first was included. Methods for data collection have been described in detail in the original study.³

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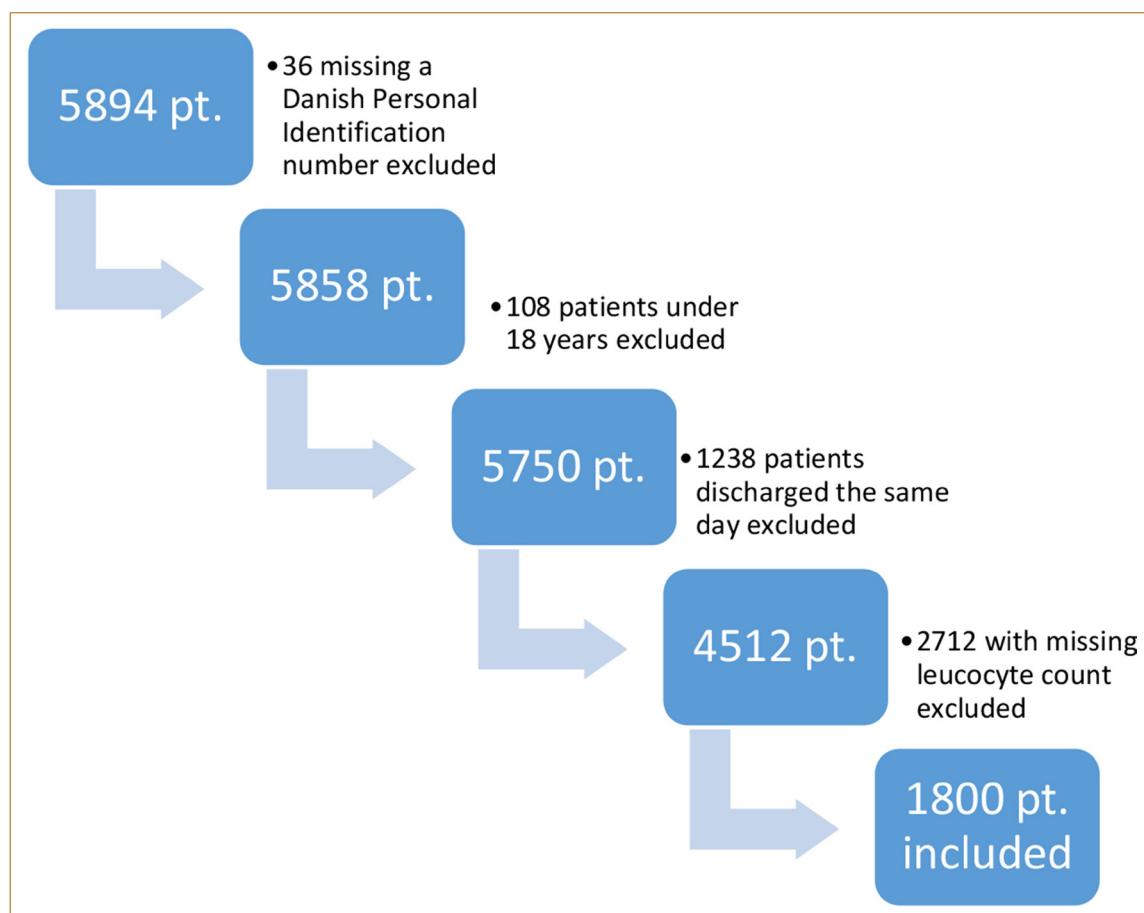


Figure 1. Inclusion/exclusion flowchart.

Inclusion/ Exclusion

Inclusion criteria was an available leucocyte count on the day of admission and the day after, minimum age of 18 years and having a Danish personal identification number.⁴ Exclusion criteria was missing leucocyte count and patients discharged the same day as admission (see Figure 1).

Statistical analysis

Patients were separated into three groups according to the development in their leucocyte count from the day of admission (day 1) to the day after (day 2). The groups were defined as:

- Fixed LC group: LC remained fixed ($\pm 3\%$).
- Decreasing LC group: LC decreased more than 3%.
- Increasing LC group: LC increased more than 3%.

The cutoff at $\pm 3\%$ was selected, because the fixed LC group would have become very small, if this group were defined as no change in the LC. The small fluctuations of $\pm 3\%$ were considered clinically irrelevant.

Data will be presented descriptively with continuous data as medians with interquartile ranges (IQR) and

categorical data as proportions (%). Significance was accepted with p-value at or beneath 0.05.

Uni- and multivariate logistic regression were performed for one-week mortality, with adjustment for potential confounding factors. The Worthington Physiological Scoring System (WPSS) and The Charlson Comorbidity Score (CCS) were used to determine how sick patients were upon admission and how this would contribute to the mortality. The WPSS is a simple validated scoring system to predict mortality in medical patients from their vital parameters with precise ‘intervention-calling scores’ which trigger interventions.⁵ The CCS is a method for classifying and scoring comorbid conditions, which might alter the risk of mortality.⁶ A score of zero indicates that no comorbidities were found.⁷ At baseline the groups were statistically different according to LC and C-reactive protein (see Table 1), and this was taken into account in the logistic regression.

Both chi-square test and logistic regression were used to determine difference in admission to the ICU and Kruskal Wallis test was performed to investigate whether LOS in the groups was different.

All statistical analysis was conducted using Stata/IC 14.0 (StataCorp, College Station, Texas, USA).

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Table 1. Baseline characteristics.

	All:	Fixed LC group:	Decreasing LC group:	Increasing LC group:	P-value:
Characteristic	n = 1800	n = 216	n = 1108	n = 476	
Age (years), median (IQR)	71 (57 – 80)	72 (55 – 80)	71 (57 – 80)	71 (58 – 81)	NS (0.80)
Women, n (%)	906 (50.3)	103 (47.7)	560 (50.5)	243 (51.0)	NS (0.70)
LC day 1 (*10 ⁹ /L), median (IQR)	10.3 (7.2 – 13.7)	9.2 (6.7 – 11.7)	11.5 (8.5 – 15.1)	8.0 (5.9 – 11)	0.0001
CRP (mg/L), median (IQR)	36 (8 – 111)	19 (3 – 75)	43 (11 – 129)	28 (6 – 94)	0.0001
Hgb (mmol/L), median (IQR)	7.9 (6.9 – 8.7)	8 (7.2 – 8.8)	7.9 (7 – 8.7)	7.8 (6.9 – 8.7)	NS (0.20)
WPSS, median (IQR)	5 (4 – 6)	5 (4 – 6)	5 (4 – 6)	5 (4 – 6)	NS (0.67)
CCS, median (IQR)	2 (0 – 3)	2 (0 – 3)	2 (0 – 3)	2 (0 – 3)	NS (0.64)

Numbers are medians with interquartile ranges (IQR) or numbers (n) and percentage (%) as appropriate.

LC: leucocyte count, CRP: C-reactive protein, Hgb: Haemoglobin, WPSS: Worthington Physiological Scoring System, CCS: Charlson Comorbidity Score.

Ethics

Approval from the Danish Data Protection Agency and the Danish Patient Safety Authority was obtained. No written informed consent was needed from participants for their clinical records to be used in this study according to Danish regulations. Patient information was anonymized and de-identified prior to analysis.

Results

Baseline characteristics of study population:

The total cohort was 5894 patients and 1800 (30.5%) remained after exclusion (see Figure 1).

Median age in the cohort was 71 years (IQR: 57 – 80), and 906 patients (50.3%) were female. The haemoglobin level was low at admission in all the groups and this correspond well with the CCS of two, which indicates that our population suffers from comorbid illnesses.

Outcome

The overall one-week mortality of the study population was 2.6%. The decreasing LC group with the lowest mortality of 1.4% and the increasing LC

group with the highest of 4.6% (see Table 2), which equals 16 and 22 patients respectively. We found significantly lower one-week mortality when LCP fell, even when controlling for sex, age, leucocyte count day 1, CRP, WPSS and CCS (see Table 3). A decreasing LC had sensitivity for one-week mortality of 65%, specificity of 62%, positive predictive value of 4% and negative predictive value of 99%. The OR for one-week mortality in the decreasing LC group compared to the fixed LC group was 0.28 (95% CI: 0.12 – 0.70).

Difference in admission to the ICU was non-significant between the three groups when performing both chi-square test and logistic regression (see Table 2). But, when performing chi-square test between the decreasing and increasing LC group, a significant difference was found (P-value of 0.018). Kruskal Wallis test for difference in length of stay between the three groups were statistically significant (see Table 2).

Sensitivity analysis:

The cutoff between the groups at 3% might not be the most optimal cutoff. When changing the cutoff from 3% to 5%, the outcomes changed very little.

Table 2. Outcomes

	All:	Fixed LC group:	Decreasing LC group:	Increasing LC group:	P-value:
Outcomes	n = 1800	n = 216	n = 1108	n = 476	
One-week mortality, n (%)	46 (2.6)	8 (3.7)	16 (1.4)	22 (4.6)	0.001
Admission to ICU, n (%)	43 (2.4)	5 (2.3)	20 (1.8)	18 (3.8)	NS (0.06)
LOS (days), median (IQR)	5 (2 – 9)	4 (1 – 8)	5 (2 – 9)	6 (3 – 10)	0.0002
30-day mortality, n (%)	129 (7.2)	17 (7.9)	61 (5.5)	51 (10.7)	0.001

Numbers are medians with interquartile ranges (IQR) or numbers (n) and percentage (%) as appropriate.

LC: Leucocyte count, ICU: Intensive care unit, LOS: Length of stay, NS: non-significant.

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Table 3. Logistic regression analyses of one-week mortality.

Groups	One-week mortality	
	Unadjusted OR (95% CI)	Adjusted ^a OR (95% CI)
Fixed LC group	1.0 (reference)	1.0 (reference)
Decreasing LC group	0.38 (0.16 – 0.90)	0.28 (0.12 – 0.70)
Increasing LC group	1.26 (0.55 – 2.88) ^b	1.11 (0.47 – 2.61) ^b

a: sex, age, leucocyte count day 1, C-reactive protein, Worthington Physiological Scoring System and Charlson Comorbidity Score. b: non-significant. OR: Odds ratio, CI: Confidence interval, LC: leucocyte count.

The biggest change was the OR for one-week mortality in the decreasing LC group, which changed from being statistically significant both before and after controlling for confounders in the analysis of the 3% cutoff groups, to only becoming statistically significant after controlling for confounders in the 5% cutoff group.

Another definition of the fixed LC group could have been maximum increase or decrease of $1.0 \times 10^9/\text{L}$ from the LC at admission. This changed the one-week mortality outcome, so that the increasing LC group got a significantly higher OR than the fixed LC group (OR: 2.6, p-value: 0.008), but the protective OR for the decreasing LC group became non-significant (OR: 0.65, p-value: 0.25).

Discussion

In this study, we compared LCP in adult patients presenting to the ED according to one-week mortality, admission to the ICU and LOS. We found the group with decreasing LC to have the lowest mortality. Overall between the three groups, there was no significant difference in the risk of being admitted to the ICU but we found a statistically significant difference in LOS between the groups.

Strengths and limitations

The strength of this study is the large study-population and the ability to have 100% follow-up, because of the unique Danish personal identification number, a ten-digit number that follow each Dane throughout their lives⁴ and the Danish civil registration system.⁸ Limitations are that our data were originally collected for another study, and many patients of the original study-population had to be excluded for this study. Furthermore, this is a single-centre study and both of these limitations weaken the external validity. All data collection was based on single, unvalidated measurements taken by ward staff as routine procedure, and as such may be prone to measurement and recording errors, but these errors would be equally distributed in the groups.

We found the group with the decreasing LC to have the lowest mortality. But, even though this group had a lower one-week mortality than the

other groups, 1.4% of these patients still die within a week. Therefore, the development in the leucocyte count might be indicative for the prognosis, but it should not stand alone. Previous studies have investigated leucocyte necrosis and apoptosis and the role of decreasing leucocytes in mortality in septic patients, and found that non-survivors had a higher amount of apoptotic leucocytes than survivors.⁹ The 1.4% who passed away in our decreasing group, might have been the septic patients. Further studies could investigate the association between LCP and the diagnosis of the patients who passed away. If there is an association between decreasing leucocyte count and sepsis, the physicians can better distinguish if a decreasing leucocyte count is a good or a bad event for this particular patient. From the analysis of sensitivity and specificity for a decreasing LC, we see that a decreasing LC is not sensitive enough to predict, nor specific enough to rule out one-week mortality. It is important for physicians to be aware of this, so the clinical assessment is not based on imprecise presumptions.

Overall between the three groups, there was no statistical significant difference in the risk of being admitted to the ICU (see Table 2). However, a statistical significant difference was found using chi-square test between the decreasing and increasing LC group, with a 2% greater risk of being admitted to the ICU if the leucocyte count increased. According to the clinical state of a patient with an increasing leucocyte count vs. a decreasing count, these results correspond with what you would expect. We found a statistically significant difference in LOS between the groups, but with a difference of only one day, from five to six days, between the decreasing and increasing group respectively (Table 3), the clinical significance is questionable. This result is surprising in contrast to the difference in admission to the ICU, because you would expect a longer hospitalization for patients with an increasing LC compared to a patient with a decreasing LC, which physicians associate with a bettering of the patients condition. You might speculate that the septic patients in the decreasing LC group are confounding the results, making the decreasing LC group clinically more

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equal to the increasing LC group and therefore reducing the differences.

This study aspired to confirm that our clinical practice of association a decreasing LC with a good prognosis was correct. Compared to a fixed and increasing LC we found that the decreasing LC was associated with a reduced one-week mortality, but still 1.4% die within a week and 5.5% die within 30 days in this group. So, it is important to be aware, that patients with a decreasing LC, may still be facing a poor prognosis, and the LCP should not be used

isolated for clinical assessment because of the low sensitivity and specificity.

Conclusion

LCP is not sensitive enough to predict, nor specific enough to rule out one-week mortality. Any physician making clinical assessments based on the LCP should be aware of this.

Conflict of Interest

Nothing to declare.

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