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ORIGINAL RESEARCH

Platelet Count within the Normal Range at Hospital Admission is Associated with Mortality in Patients with Community-Acquired Pneumonia

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Background: Apart from their hemostatic role, platelets are immune cells that play a role in fighting infections. The presence of thrombocytopenia and thrombocytosis at hospital admission are predictors of mortality in community-acquired pneumonia patients. We hypothesized that variations in platelet counts within the normal range also may be associated with mortality in these patients.

Methods: The study included all adults in the North and Central Denmark Regions with a first acute hospital admission for community-acquired pneumonia during 2006–2012. We assessed the association between the first platelet count within ± 24 hours of admission (within the normal range of 150 to 400 x 10^9/L) and 30-day mortality using Cox models. Analyses were adjusted for age, sex, Charlson Comorbidity Index score, hemoglobin level, leukocyte count, and creatinine level at admission.

Results: Among the 12,905 study patients, 30-day mortality was 12.4%. The mean platelet count upon admission was 250 × 10^9/L. Compared with the 250–275 × 10^9/L category, platelet counts of 151–175 were associated with a lower 30-day mortality (adjusted hazard ratio [aHR]: 0.79, 95% confidence interval [CI]: 0.63–0.99), while higher platelet counts were associated with a higher 30-day mortality (351–375 × 10^9/L, aHR: 1.34, 95% CI: 1.07–1.68; 376–400× 10^9/L, aHR: 1.21, 95% CI: 0.94–1.56).

Conclusion: Platelet counts, even within the normal range, are associated with mortality in adult patients hospitalized for community-acquired pneumonia.

Keywords: platelet count, thrombocytopenia, thrombocytosis, community-acquired pneumonia, mortality

Introduction

Apart from their role in hemostasis, platelets have pleiotropic effects. They are involved in the regulation of inflammation, stress, and the immune response.[1–3] Consequently, platelets play a role in host defense against infections, including community-acquired pneumonia (CAP).[4]

In patients admitted for CAP, thrombocytopenia at the time of admission (platelet count <100 × 10^9/L) has been associated with a higher rate of complications[5] and of 30-day mortality.[6,7] A platelet count <150 × 10^9/L at admission has been associated with higher mortality in patients admitted to an intensive care unit (ICU) for CAP.[8] At the same time, a platelet count at admission ≥400 × 10^9/L has been associated with death in patients hospitalized with CAP.[7] However, no studies examined the association of platelet counts within the normal range (150–400 × 10^9/L) with mortality.

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Methods

Setting and Design

This cohort study was conducted using Danish population-based medical registries. In Denmark, tax-funded health care guarantees free access to hospital care to all Danish residents. A unique identifier assigned to each resident at birth or upon immigration allows unambiguous linkage of data for all patients receiving care from the Danish National Health Service.[9]

Data Source

We used the Danish National Patient Registry (DNPR) to identify all hospital admissions for CAP in the North and Central Denmark Regions (population = 1.8 million persons) from January 1, 2006 to December 31, 2012. The study period was selected based on the availability of complete data in the clinical laboratory information system database (LABKA), which covers the entire study area.[10]

The DNPR contains records for all admissions to Danish non-psychiatric hospitals since 1977 and for all emergency department and outpatient clinic visits since 1995.[11] At least one primary discharge diagnosis is recorded in the DNPR for every inpatient stay and outpatient visit. Since 1994, these diagnoses have been coded using the International Classification of Diseases, Tenth Revision (ICD-10).[12]

Study Cohort

Study inclusion criteria were (i) adult age (defined as age >15 years at hospital admission); (ii) a hospitalization in the North or Central Denmark Regions during the study period with a discharge diagnosis of pneumonia (index admission); (iii) no hospitalization recorded within 90 days prior to the index admission (required to ascertain community-acquired illness); and (iv) availability of a platelet count measurement at hospital admission (time of admission ± 24 hours). We identified pneumonia among discharge diagnoses using ICD-10 codes J12-J18. These codes were found to have a very high positive predictive value in two independent studies in the DNPR (90.0%, 95% confidence interval – CI: 82.0–95.0% and 92.9%, 95% CI: 68.5–98.7%, respectively).[13,14] For each identified patient, only the first acute hospital admission during the study period was considered in the analyses.

Platelet Counts

Platelet count measurements were obtained from the LABKA database. This database contains results of all tests performed on blood samples drawn from hospital inpatients and outpatients and submitted to hospital laboratories in the Northern and Central Denmark regions since 2006.[10] We restricted the study population to patients with a normal platelet count (150–400 × 10^9/L).

Mortality

We assessed the 30-day mortality rate. Vital status and date of death (if applicable) were ascertained from the Danish Civil Registration System, which is updated daily and ensures complete follow-up.[9]

Covariates

Covariates were: age (<65 versus ≥65 years), sex, Charlson Comorbidity Index (CCI) score categories (0, 1–2, ≥3), hemoglobin level at admission (categorized as normal: ≥12 g/dL in women and ≥13 g/dL in men; mild anemia: 10–11.9 g/dL in women and 10–12.9 g/dL in men; and severe anemia: <10 g/dL), leukocyte count at admission (categorized as leukopenia: <4 x 10^9/L; normal: 4–11 x 10^9/L; and leukocytosis: >11 x 10^9/L), and creatinine level at admission (≥1.5 mg/dL versus <1.5 mg/dL). The CCI score has been associated with mortality in the setting of hospitalized patients.[15] Comorbidities included in the CCI were identified using hospital inpatient and outpatient diagnoses prior to the index hospitalization, as recorded in the DNPR. These DNPR diagnoses have been validated previously.[16] ICD-10 codes used to identify comorbidities are listed in Table S1.

Statistical Analyses

We used Cox regression models to assess the association between platelet count at the time of hospital admission and 30-day mortality. In the case of several platelet count measurements at the time of admission ± 24 hours, we considered the first one. Normal platelet counts were categorized by 25 x 10^9/L intervals, using the 251–275 x 10^9/L as reference. We also assessed the platelet count as a continuous variable, by subgroups of two categories (≤275 x 10^9/L vs >275 x 10^9/L). All analyses were adjusted for the covariates listed above. Statistical analyses were performed using SAS V9.4™ software (SAS Institute, Cary, NC, USA).

Ethical Considerations

In accordance with Danish law, we obtained permission from the National Data Protection Agency for this study

(Record no. 2015–57-0002, Aarhus University record no. 2016–051-000001/396).[17]

Results

Population

Among 37,239 adult patients hospitalized with pneumonia during 2006–2012, 29,076 (78.1%) had a platelet count recorded at admission, including 23,549 patients whose count was within normal values. There was no difference in terms of characteristics and of 30-day mortality between the patients with platelet count measurement at admission and those without (Table S2). The final study population consisted of 12,905 adult patients with no hospitalization recorded within 90 days prior to the index admission and who had a normal platelet count at admission. Patients' characteristics are shown in Table 1. The median age was 73.2 years (first quartile: 58.7 years; third quartile: 83.1 years), 6593 (51.1%) were men, and 8214 (63.6%) had at least one CCI comorbidity. Mean platelet count was 248 x 10^9/L (standard deviation: 72.5 x 10^9/L). Within the first 48 hours following admission, 506 (3.9%) were admitted to an intensive care unit and 214 (1.7%) needed mechanical ventilation.

Table 1 Characteristics of 12,905 Adult Patients Hospitalized for Community-Acquired Pneumonia Who Had Normal Platelet Counts at Admission, North and Central Denmark, 2016–2012

Variables	Values
Median age (Q1-Q3), years	73.2 (58.7–83.1)
Age ≥65 years, n (%)	8403 (65.1)
Men, n (%)	6593 (51.1)
Charlson Comorbidity Index score	
0, n (%)	4691 (36.3)
1–2, n (%)	5035 (39.0)
>2, n (%)	3179 (24.6)
Mean platelet count at admission, × 10^9/L (standard deviation)	248 (72.5)
Hemoglobin level at admission	
Normal (≥12 g/dL in women and ≥13 g/dL in men), n (%)	7984 (61.9)
Mild anemia (10–11.9 g/dL in women and 10–12.9 g/dL in men), n (%)	4205 (32.6)
Severe anemia (<10 g/dL), n (%)	701 (5.4)
Leukocyte count at admission	
Normal (4–11 10^9/L), n (%)	6353 (49.3)
Leukopenia (<4 × 10^9/L), n (%)	169 (1.3)
Leukocytosis (>11 10^9/L), n (%)	6373 (49.4)
Creatinine level at admission ≥1.5 mg/dL, n (%)	1779 (13.8)
Admission to intensive care unit within the first 48 hours, n (%)	506 (3.9)
Mechanical ventilation	214 (1.7)

Association Between Normal Platelet Count at Admission and 30-Day Mortality

Thirty-day mortality was 12.4% (1601 patients). Results of the Cox regression model are presented in Table 2. Platelet counts inferior to the mean value were associated with a lower 30-day mortality while platelet counts superior to the mean value were associated with a higher 30-day mortality. The size of the effect was maximal for platelet counts between 151 and 175, which were associated with a lower 30-day mortality as compared with the 251–275 × 10^9/L category (adjusted hazard ratio – aHR: 0.79, 95% CI: 0.63–-0.99), and for platelet counts of 351–375 x 10^9/L which were associated with a higher 30-day mortality (aHR: 1.34, 95% CI: 1.07–1.68). Analyses considering the platelet count as a continuous variable confirmed this trend.

Discussion

Our study showed that even within the normal range, platelet counts at hospital admission were associated with mortality with an asymmetrical association compared to the mean: platelet counts high within the normal range (351–375 x 10^9/L) predicted increased mortality while platelet counts low within the normal range (151–175 x 10^9/L) predicted decreased mortality.

A previous US study in 500 patients hospitalized for CAP previously suggested that platelet counts between 350 and 400 × 10^9/L were associated with higher 30-day mortality.[6] Such elevated platelet counts compared with the mean may reflect a severe inflammatory process[18] with poorer prognosis.[19] Such platelet counts also may be linked to increased occurrence of local complications (empyema or pleural effusion with more inflammation)[7] or cardiovascular complications (due to inflammation and increased platelet activation)[20] in CAP patients.

Thrombocytopenia in infected patients can be due to hemodilution, platelet consumption, impaired platelet production, or hypersplenism.[21] Biomarkers involved in both sepsis and platelet physiology have been assessed. They were clustered in biomarkers related to platelet activation, innate immunity and endothelial dysfunction, adaptative immunity and repair, thrombopoiesis, and cell death. The

Table 2 Association Between Normal Platelet Counts at Acute Hospital Admission and 30-Day Mortality in Adult Patients Hospitalized for Community-Acquired Pneumonia Whose Platelet Counts Were Normal at Admission, North and Central Denmark, 2016–2012 (Cox Regression Model)

Platelet Count	Death at Day 30, n (%)	Adjusted Hazard Ratio (95% Confidence Interval)[a]
By categories		
151–175 × 10^9/L, n=1266	123 (9.7)	0.79 (0.63–0.99)
176–200 × 10^9/L, n=1640	189 (11.5)	0.94 (0.77–1.14)
201–225 × 10^9/L, n=1725	190 (11.0)	0.90 (0.74–1.10)
226–250 × 10^9/L, n=1769	208 (11.8)	0.95 (0.78–1.16)
251–275 × 10^9/L, n =1577	193 (12.2)	reference
276–300 × 10^9/L, n =1412	184 (13.0)	1.07 (0.88–1.31)
301–325 × 10^9/L, n =1165	158 (13.6)	1.11 (0.90–1.37)
326–350 × 10^9/L, n =989	145 (14.7)	1.21 (0.98–1.50)
351–375 × 10^9/L, n =757	122 (16.1)	1.34 (1.07–1.68)
376–400 × 10^9/L, n =605	89 (14.7)	1.21 (0.94–1.56)
As a continuous variable		
150–275 × 10^9/L, for every 10 × 10^9/L decrease, n=7977	903 (11.3)	0.98 (0.96–1.00)
276–400 × 10^9/L, for every 10 × 10^9/L increase, n =4928	698 (14.2)	1.01 (0.99–1.03)

Notes: [a]Adjusted for age, sex, Charlson Comorbidity Index score, hemoglobin level, leukocyte count, and creatinine level at admission.

platelet count was correlated with thrombopoiesis growth factors, innate immunity/endothelial dysfunction, and platelet activation biomarkers.[22] Moreover, pneumococcus directly promotes platelet activation and aggregation.[4] Therefore, thrombocytopenia is usually thought to reflect infection severity associated with higher mortality, including in CAP patients.[6,7]

We observed that slight variations from the mean due to all the factors mentioned above, still within the normal range of platelet count, are associated with mortality. Our finding of lower mortality among patients with a platelet count low within the normal range compared with the mean (150 to 174 x 10^9/L) may reflect platelet consumption related to their activation as innate immune system effectors in controlling the infection.[1,3,18]

These findings should be assessed within the limitations of our study. First, the study reflects routine clinical care. Thus, only 78.1% of patients had a platelet count recorded at hospital admission. However, there was no significant difference in baseline characteristics and mortality rates between the patients with and without platelet count measurements in this study, suggesting no major bias due to missing platelet counts. Selection bias due to coding errors of diagnoses is also unlikely, as coding is accurate in the DNPR, particularly for pneumonia.[12–14] Second, lack of some clinical and laboratory data such as arterial pressure, confusion, respiratory rate, or urea (in the calculation of the CURB-65 – confusion, urea, respiratory rate, blood pressure, and age – score) prevented subgroup analyses focusing on disease severity. Unfortunately, the number of patients admitted to intensive care units was too small to allow a separate analysis. Third, we did not assess some other platelet parameters that may influence mortality like the mean platelet volume[25] of variations of the platelet count during hospitalization.[26] Fourth, we could not stratify the analyses by pathogen, due to the lack of microbial documentation in the database. Our study could thus not address variations by specific subgroups. Lastly, this is the first study investigating the association between the platelet count within the normal range upon admission and 30-day mortality in this setting, and these results must be confirmed in other cohorts.

Conclusion

This study emphasizes that normal platelet counts upon acute hospital admission are relevant prognostic biomarkers that may help clinicians assess the clinical course of adult patients hospitalized for CAP. Moreover, the lower mortality observed in patients with platelet counts between 151 and 175 x 10^9/L may reflect the appropriate involvement of platelets in host defense against pathogens, opening the door for future studies elucidating the role of platelet involvement in CAP patients.

Abbreviations

CAP, community-acquired pneumonia; CCI, Charlson Comorbidity Index; DNPR, Danish National Patient Registry; ICD-10, International Classification of Diseases, Tenth Revision; ICU, intensive care unit.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

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References

1. Morrell CN, Aggrey AA, Chapman LM, Modjeski KL. Emerging roles for platelets as immune and inflammatory cells. *Blood*. 2014;123(18):2759–2767. doi:10.1182/blood-2013-11-462432
2. Xu XR, Zhang D, Oswald BE, et al. Platelets are versatile cells: new discoveries in hemostasis, thrombosis, immune responses, tumor metastasis and beyond. *Crit Rev Clin Lab Sci*. 2016;53(6):409–430. doi:10.1080/10408363.2016.1200008
3. Parikh F. Infections and Thrombocytopenia. *J Assoc Physicians India*. 2016;64(2):11–12.
4. Anderson R, Feldman C. Review manuscript: mechanisms of platelet activation by the pneumococcus and the role of platelets in community-acquired pneumonia. *J Infect*. 2017;75(6):473–485. doi:10.1016/j.jinf.2017.09.013
5. Aliberti S, Amir A, Peyrani P, et al. Incidence, etiology, timing, and risk factors for clinical failure in hospitalized patients with community-acquired pneumonia. *Chest*. 2008;134(5):955–962. doi:10.1378/chest.08-0334
6. Mirsaeidi M, Peyrani P, Aliberti S, et al. Thrombocytopenia and thrombocytosis at time of hospitalization predict mortality in patients with community-acquired pneumonia. *Chest*. 2010;137(2):416–420. doi:10.1378/chest.09-0998
7. Prina E, Ferrer M, Ranzani OT, et al. Thrombocytosis is a marker of poor outcome in community-acquired pneumonia. *Chest*. 2013;143(3):767–775. doi:10.1378/chest.12-1235
8. Brogly N, Devos P, Boussekey N, et al. Impact of thrombocytopenia on outcome of patients admitted to ICU for severe community-acquired pneumonia. *J Infect*. 2007;55(2):136–140. doi:10.1016/j.jinf.2007.01.011
9. Schmidt M, Pedersen L, Sørensen HT. The Danish civil registration system as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541–549. doi:10.1007/s10654-014-9930-3
10. Grann AF, Erichsen R, Nielsen AG, Frøslev T, Thomsen RW. Existing data sources for clinical epidemiology: the clinical laboratory information system (LABKA) research database at Aarhus University, Denmark. *Clin Epidemiol*. 2011;3:133–138. doi:10.2147/CLEP.S17901
11. Lynge E, Sandegaard JL, Rebolj M. The Danish national patient register. *Scand J Public Health*. 2011;39(7 Suppl):30–33. doi:10.1177/1403494811401482
12. Schmidt M, Schmidt SAJ, Sandegaard JL, et al. The Danish national patient registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449–490. doi:10.2147/CLEP.S91125
13. Thomsen RW, Riis A, Nørgaard M, et al. Rising incidence and persistently high mortality of hospitalized pneumonia: a 10-year population-based study in Denmark. *J Intern Med*. 2006;259(4):410–417. doi:10.1111/j.1365-2796.2006.01629.x
14. Ingeman A, Andersen G, Hundborg HH, Johnsen SP. Medical complications in patients with stroke: data validity in a stroke registry and a hospital discharge registry. *Clin Epidemiol*. 2010;2:5–13. doi:10.2147/CLEP.S8908
15. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373–383. doi:10.1016/0021-9681(87)90171-8
16. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish national registry of patients. *BMC Med Res Methodol*. 2011;11:83. doi:10.1186/1471-2288-11-83
17. Ludvigsson JF, Håberg SE, Knudsen GP, et al. Ethical aspects of registry-based research in the Nordic countries. *Clin Epidemiol*. 2015;7:491–508. doi:10.2147/CLEP.S90589
18. Elzey BD, Sprague DL, Ratliff TL. The emerging role of platelets in adaptive immunity. *Cell Immunol*. 2005;238(1):1–9. doi:10.1016/j.cellimm.2005.12.005
19. Antunes G, Evans SA, Lordan JL, Frew AJ. Systemic cytokine levels in community-acquired pneumonia and their association with disease severity. *Eur Respir J*. 2002;20(4):990–995. doi:10.1183/09031936.02.00295102
20. Rae N, Finch S, Chalmers JD. Cardiovascular disease as a complication of community-acquired pneumonia. *Curr Opin Pulm Med*. 2016;22(3):212–218. doi:10.1097/MCP.0000000000000261
21. Greinacher A, Selleng SS. I evaluate and treat thrombocytopenia in the intensive care unit patient. *Blood*. 2016;128(26):3032–3042. doi:10.1182/blood-2016-09-693655
22. Bedet A, Razazi K, Boissier F, et al. Mechanisms of thrombocytopenia during septic shock: a multiplex cluster analysis of endogenous sepsis mediators. *Shock*. 2018;49(6):641–648. doi:10.1097/SHK.0000000000001015
23. Moulis G, Christiansen CF, Darvalics B, Nørgaard M. Prevalence of thrombocytopenia and thrombocytosis upon acute hospital admission to internal medicine units. A cross-sectional study in Denmark. *Eur J Intern Med*. 2018;57:e34–e37. doi:10.1016/j.ejim.2018.08.014
24. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. 2003;58(5):377–382. doi:10.1136/thorax.58.5.377
25. Gorelik O, Tzur I, Barchel D, et al. A rise in mean platelet volume during hospitalization for community-acquired pneumonia predicts poor prognosis: a retrospective observational cohort study. *BMC Pulm Med*. 2017;17(1):137. doi:10.1186/s12890-017-0483-6
26. Gorelik O, Izhakian S, Barchel D, et al. Prognostic significance of platelet count changes during hospitalization for community-acquired pneumonia. *Platelets*. 2016;1–7.