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Original Article

Hematologic Indices and Chronic Subdural Hematoma: A Single-Center Cohort Study

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Abstract

Objective Chronic subdural hematoma (cSDH) is common, predominantly affects the elderly, often recurs after treatment, and can have serious complications, including death. Inflammation plays an important role in cSDH and it has been previously shown that some laboratory indices are useful as prognostic markers. The aim was to research the role of hematologic and inflammatory markers in cSDH.

Materials and Methods A single-center archival database review to retrieve data on cSDH cases operated on between 2018 and 2020, including: (1) sociodemography (age, gender), (2) clinics (Glasgow Coma Score [GCS], anticoagulants, chronic conditions), (3) laboratory (leukocyte, neutrophil, platelet, C-reactive protein, hemoglobin, red cell distribution width [RDW], neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio [PLR], systemic immune-inflammatory index [SII]), (4) cSDH (size, location, midline shift), and (5) treatment (craniotomy/craniostomy, drainage). Primary outcome was Glasgow Outcome Score (GOS) at discharge and at 1 year, and secondary outcomes were 1 year mortality, resurgery, and recurrence. Hematological and inflammatory indices were compared across two cSDH thickness groups.

Results Seventy-two patients were included, 25 women and 47 men, median age 77 years. Seventeen (23.6%) patients had chronic anticoagulant treatment. The majority had a chronic comorbidity: 19 (26.4%) diabetes, 48 (66.7%) hypertension, and 56 (77.8%) other chronic diseases. Median preoperative GCS was 15. Median cSDH thickness was 22.9 mm, sidedness was equally distributed, and midline shift occurred in 60 (83.3%) patients, with median midline shift of 8.4 mm. The majority of patients underwent a single craniostomy ($n = 44$, 61.1%), and in all patients a subdural drainage was placed. Median GOS at discharge and at 1 year postoperatively was 5. Mortality was 11.1%, and 16.7% of patients were lost to follow-up. Within the 1-year follow-up, 27.8% of patients had disease recurrence, 25% underwent a repeat surgery. In the "above" versus "below" 15 mm cSDH thickness group there were

Keywords
- chronic subdural hematoma
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- hematopoiesis
- outcome
- surgery

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significant differences in P count (211.5 vs. 279.5 $\times 10^9$/L, $p = 0.009$), RDW (13.3 vs. 12.6, $p = 0.031$), SII (1782 vs. 2653, $p = 0.025$), and PLR (26.2 vs. 36.7, $p = 0.042$).
Conclusion Hematological indices bear a diagnostic and prognostic potential in cSDH management.

Introduction

Chronic subdural hematoma (cSDH) is a common neurosurgical entity, seen predominantly in the elderly population. Owing to rising life expectancy and increase in use of anticoagulant/antithrombotic agents, the incidence of cSDH has been on the rise.[1] Its exact etiopathogenesis remains to be elucidated, yet trauma and inflammation seem to play an important role.[1] Of all diagnosed cSDH cases only a proportion will require surgical evacuation via one of three procedures—a craniotomy, single, or double craniostomy. Which patients are best suited for which of the procedures is often debatable and clear empirical evidence is yet to be established.[2]

Recurrence is a major issue in cSDH surgery, regardless of the type of procedure, with a summary estimate of 13%, with some studies reporting up to 33% of cases recurring.[3] Different factors are known to be associated with cSDH surgery and outcome, such as preoperative clinical performance, anticoagulant use, age, midline shift, hematoma thickness and density, etc., and scoring systems have been devised with the intent to enable outcome prognostication.[4–6]

Standard hematological indices, including peripheral blood inflammatory markers as well as their different ratios, have been shown to be associated with disease severity and outcome across a wide spectrum of acute and chronic surgical and nonsurgical conditions.[7–13] Some of the indices and ratios have also been investigated for their role in cSDH pathogenesis and prognosis: for example, cell counts, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) were found to be associated with cSDH recurrence.[14–16] However, the association between other standard indices and ratios and cSDH severity remain to be researched, which is the aim of this study.

Materials and Methods

The study was approved by the Institutional Review Board.

Study Design and Setting

This was an observational retrospective cohort study in which the institutional patient archive was retrospectively reviewed for all cSDH cases operated on at our department between January, 2018 and December, 2019.

Patients

Adult patients with a radiologically proven cSDH who underwent surgical treatment were included. Patients were considered ineligible if their records were incomplete with regard to outcomes or baseline characteristics.

Variables

For each patient these variables were collected: (1) sociodemographic data (age, gender); (2) clinical data (Glasgow Coma Score [GCS], anticoagulants, chronic conditions); (3) laboratory data (leukocyte [L], neutrophil [N], and platelet [P] count, C-reactive protein [CRP] levels, red-cell distribution width [RDW], NLR, PLR, and systemic immune-inflammatory index [SII]), (4) cSDH data (size, laterality, midline shift); and (5) treatment-related data (craniotomy or craniostomy—single or double, subdural drainage use). Primary outcome was clinical outcome at discharge and at 1 year (assessed by Glasgow Outcome Scale [GOS]), and secondary outcomes were 1 year mortality, resurgery, and recurrence.

Data Sources

GCS is routinely assessed at admission and was copied from patient forms. GOS at discharge and 1 year postoperatively was assessed from data available in the digital archive (operating room forms, neurosurgery intensive care unit forms and discharge letter, neurosurgery ward forms and discharge letters, neurosurgery outpatient clinic forms). Anticoagulant use was defined as patients having at least 1 month use of anticoagulants (vitamin K antagonists, direct oral anticoagulants, low-molecular-weight heparin) or antithrombotics (aspirin, clopidogrel, or newer antithrombotic drugs). A patient was considered to be suffering from a chronic condition if history was positive for a chronic condition that is known to impact surgery/anesthesia outcome. This included diabetes, heart failure, previous myocardial infarction, kidney failure, liver failure, chronic obstructive lung disease, autoimmune diseases, etc. Cell counts (L, N, P), hemoglobin (Hgb), CRP, and RDW values were copied from patient charts and these indices were used to calculate the NLR, PLR, and SII (calculated as $P \times N/L$). All laboratory analyses were performed at the Department of Laboratory Diagnostics, Clinical Hospital Center Zagreb, Zagreb, Croatia. Radiological variables were independently assessed by two researchers on the images available from the institutional Picture Archiving and Communication System and checked against the official report from the Department of Radiology. cSDH size was measured in mm, at its largest diameter, from inner tabula of the neurocranium to the cortex, two times per researcher, and an average of the two values was considered for analyses. Midline shift was assessed at the level of foramen of Monro in the same manner as cSDH size. All variables were coded into numerical values and entered into a prespecified sheet.

Preoperative, intraoperative, and postoperative care were performed in a standard manner for all patients. In general,

the policy at our department is to perform all cSDH procedures under general anesthesia, by doing a craniostomy (single or double) and use drainage. In cases which have septae within the cSDH, have a hyperdense content of the cSDH (i.e., acutization), evidence of intraoperative subdural bleeding, or recurrence, a craniotomy is considered. However, the final decision on the choice of treatment is made by the attending surgeon.[17]

Statistical Analysis

Distribution normality was assessed graphically (QQ plots) and using the Shapiro–Wilk test. Continuous variables were summarized as mean (95% confidence interval) or median (interquartile range), categorical variables as absolute (relative) frequencies. Pairwise comparisons were made between groups with regard to dichotomized clinical outcome at 1 year postoperatively (GOS ≥ 4 = good vs. GOS ≤ 3 = bad). Finally, the sample was divided into two groups with regard to hematoma thickness, with 15 mm set as cutoff value.[18] Medians of hematological indices and ratios were compared across the two groups using the Mann–Whitney *U* test.

Results

Patients

In the observed period, we were able to identify 72 patients who met the inclusion criteria. Of those, 25 were women and 47 men; median age was 77 years (range = 38–94 years). Seventeen (23.6%) patients had chronic anticoagulant treatment: 12 (16.7%) on warfarin, 4 (5.6%) on direct oral anticoagulants, and 1 (1.4%) on low-molecular-weight heparin. The majority had a chronic comorbidity: 19 (26.4%) had diabetes, 48 (66.7%) hypertension, and 56 (77.8%) other chronic diseases. Median preoperative GCS was 15. Patient data are summarized in ►**Table 1**.

Radiological Features

Median cSDH thickness was 22.9 mm, and sidedness was roughly equally distributed between left, right, and bilateral. A midline shift occurred in 60 (83.3 %) patients, and median size of midline shift was 8.4 mm. Radiological features are summarized in ►**Table 1**.

Surgical Data

The majority of patients underwent a single craniostomy ($n = 44$, 61.1%), and in all patients a subdural drainage was placed. Surgical data is summarized in ►**Table 1**.

Outcomes

Median GOS at discharge and at 1 year postoperatively was 5. Mortality was 11.1%, and 16.7% of patients were lost to follow-up. Within the 1-year follow-up, 27.8% of patients had disease recurrence, and 25% underwent a repeated surgery. Outcomes are summarized in ►**Table 1**.

Hematological Indices and Ratios

Hematological indices and ratios were compared between the two subgroups of patients with regard to cSDH thickness.

Table 1 Summary of clinical, radiological, and surgical findings and outcomes

Variable	μ	Range/%
Glasgow Coma Score	15	3–15
Direct oral anticoagulants	4	5.6
Warfarin	12	16.7
Low molecular weight heparin	1	1.4
Diabetes	19	26.4
Hypertension	48	66.7
Other chronic disease	56	77.8
cSDH thickness (mm)	22.9	21.4; 24.5
Laterality – left/right/bilateral	26/25/21	36.1/34.7/29.2
Midline shift (yes)	60	83.3
Midline shift size	8.4	1.5-21-2
Craniotomy/single craniostomy/double craniostomy	3/44/25	4.2/61.1/34.7
Drainage	72	100
Deceased/alive/lost to follow-up	8/52/12	11.1/72.2/16.7
1 year recurrence (n/y/m/l)	45/20/1/6	62.5/27.8/1.4/8.3
1 year resurgery (n/y/l)	48/18/6	66.7/25/8.3
Glasgow Outcome Score	5	2–5
1 year Glasgow Outcome Score	5	1–5

Abbreviations: cSDH, chronic subdural hematoma; l, loss to follow-up; m, multiple; n, no; y, yes.
Note: Numbers are median (range) or absolute (relative) frequency.

Table 2 Summary of hematological indices and ratios

Variable	Overall		cSDHt > 15 mm ($n = 66$)		cSDHt < 15 mm ($n = 6$)		*p*-Value
	μ	Range/%	μ	Range/%	μ	Range/%	
L ($\times 10^9$/L)	8.1	3.5–17	8.1	3.5–17.0	8.5	5.5–13-2	0.960
N (%)	70.2	41.4–93.3	71.7	41.4–93.3	68.7	61.5–78.4	0.897
P ($\times 10^9$/L)	220.5	47–897	211.5	47–897	279.5	254–412	0.009*
CRP (mg/L)	4.2	0.3–473.7	4.1	0.3–473.7	7.5	0.8–25.2	0.945
RDW	13.3	11.6–19.9	13.3	11.6–19.9	12.6	12.1–14.4	0.031*
Hemoglobin (g/L)	128.5	66–160	128.5	66–160	134	93–155	0.728
SII	1789	841–3790	1782	841–3790	2653	1552–3176	0.025*
NLR	8.3	4.3–19.4	8.3	4.3–19.4	8.8	5.8–11.2	> 0.999
PLR	26.3	10–53.4	26.2	10–53.4	36.7	23.3–51.6	0.042*

Abbreviations: CRP, C-reactive protein; cSDH, chronic subdural hematoma; L, leukocytes; N, neutrophils; NLR, neutrophil-to-lymphocyte ratio; P, platelet; PLR, platelet-to-lymphocyte ratio; RDW, red cell distribution width; SII, systemic immune-inflammatory index.
Note: Numbers are median (range) or absolute (relative) frequency.
*statistically significant.

With the cutoff set at 15 mm, there were 66 patients with a cSDH thickness above the cutoff, and 6 patients below the cutoff. In the "above" versus "below" comparisons there were significant differences in P count (211.5 vs. 279.5×10^9/L, $p = 0.009$), RDW (13.3 vs. 12.6, $p = 0.031$), SII (1782 vs. 2653, $p = 0.025$), and PLR (26.2 vs. 36.7, $p = 0.042$). There were no significant differences in leukocyte and neutrophil counts, CRP and Hgb levels, and NLR. Data on hematological indices and ratios are summarized in ►**Table 2**.

Discussion

The aim of this study was to assess routine hematological indices and their ratios in patients with cSDH undergoing surgical treatment. The main findings of this study suggest that some of the indices are associated with disease severity, thereby having diagnostic and prognostic potential.

Our cohort of 72 patients is comparable in terms of socio-demographic data as previously published data. Authors of a recent nationwide-based study on 8,539 patients from Finland reported an average age of 73 ± 12.8 years, and the majority (68%) of the patients were male.[19] An earlier study from Spain reported an almost matching cohort, with an average age of 72.7 ± 11.4 years, and 62.8% males.[20] Our results fall in line with these, as the median age of our patients was 77 years, and the proportion of men was 65.3%. Given this data, the observed proportion of comorbidities and use of anticoagulant drugs in our cohort is not surprising and falls in line with the generally observed rising trends in prevalence in comorbidity among adults and associated rising trends of anticoagulant usage.[1,21–24] The dynamics of both of these trends is important when considered from the perspective of cSDH incidence, treatment, and outcomes, as comorbidities dramatically increase cSDH surgery fatality, and anticoagulants have an established causative role in cSDH.[19,25] As the population ages, and the demographic landscape is expected to change dramatically in the coming decades, these factors (growing incidence accompanied by growing incidence of aggravating factors) might render cSDH an important future challenge for the neurosurgical, but also global medical, community.[26] Indeed, what was once considered a trivial disease is now seen as being associated with significant excess mortality and thus posing a significant societal burden.[19]

The majority (61.1%) of our patients underwent a single craniostomy, a minor proportion a double craniostomy (34.7%), and craniotomy was exceptional (4.2%). All patients received a subdural drainage. Why, when, and how to operate on a cSDH remains debatable to this day.[2] Less debatable is the role of observation and conservative treatment, as research continues to fail to show its superiority over surgical evacuation.[20] Among the surgical options, craniostomy has long surpassed craniotomy as the method of choice, the latter being reserved for complicated and recurrent cases.[2,27] Adjunct techniques, such as neuroendoscopy, have also been reported, yet they have not entered standard use, despite earlier introduction into clinical practice.[28] Bearing in mind the differing indications for the two surgical procedures, the differences in outcomes are expected, since craniotomy (the more extensive option) is used in more difficult cases. Indeed, it has been shown that craniotomy is clinically and economically inferior over craniostomy.[2,27]

In our series, 1 year mortality was 11.1%, an important piece of information to be considered alongside a caveat that 16.7% of cases were lost to follow-up. If we consider a halfway point between the two extremes, the outcome in our cohort is comparable to the data from the Finnish study, where 1-year case–fatality rates were 14 and 15% for men and women, respectively.[19] On the other hand, if all of the cases lost to follow-up were actually fatalities, then mortality in our cohort is substantially higher. At the same time, this upper estimate would be comparable to one reported in a study from the United Kingdom (1-year fatality of 25.9%), and lower than that from the United States (32 and 30%).[29–31] Regardless of how we interpret the loss-to-follow-up, the

fact itself points to a need for a nationwide registry dedicated to following outcomes of not only cSDH cases, but also other neurosurgical entities and beyond. The same issue, namely, one of inadequate nationwide disease monitoring, we found when investigating the epidemiology of neoplasms of the central nervous system. Therefore, the issue seems to be systematic and in need of urgent addressment.[32] One year recurrence and resurgery rates in our cohort were 27.8 and 25%, respectively, with a loss-to-follow-up of 8.2%. These rates are somewhat higher than the recently published range between 10 and 20%.[19] These facts add to the severity of the problem on a global scale, since even the most conservative estimates show that cSDH, a "benign" condition, carries a prognosis far more dismal than many other malignant neurosurgical entities. Indeed, median posttreatment cSDH survival depicts the severity of the condition and its status should be reconsidered and treated with proper recognition.[30,31]

The main aim of this study was to investigate the association between hematological indices and their ratios and cSDH severity. We did this by comparing cell counts, CRP, Hgb, RDW, SII, NLR, and PLR between patient groups with cSDH thickness higher or lower than 15 mm. We found that patients with larger cSDH have a significantly higher RDW, lower P counts, SII, and PLR. We interpret the result, albeit with caution, due to small sample size, as indicating that cSDH severity might be associated with higher RDW values and lower P counts. Both of the significantly lower ratios (SII and PLR) include P count in the numerator, therefore they are in the same direction as the P counts. This same constellation, namely, that of a high RDW and low P count, was shown to be associated with survival (i.e., severity) in lymphoma.[33] The association between the low P count and cSDH thickness (severity) in the setting of high RDW observed in our cohort might be interpreted in two ways. First, the cSDH in itself strains the organism, including hematopoiesis, thus reducing the ability to produce sufficient quantities of thrombocytes (i.e., their precursors), subsequently leading to thrombocytopenia and at the same time to produce sufficient quantities of mature red blood cells, resulting in widening of the RDW. The association between RDW and disease prognosis is an established fact across a wide spectrum of pathological entities. It is an indicator of systemic inflammatory responses and was shown to be a useful prognostic and diagnostic marker even in the general population. However, its role in cSDH formation, sustainment, progression, and prognosis remains poorly investigated.[33,34] Second, thrombocytopenia-associated coagulopathy sustains cSDH growth. This interpretation is supported by the established role of coagulopathy in cSDH etiology.[1] Regardless of the order in which they occur, we believe the phenomenon points to an etiopathogenetic interplay between hematopoiesis and cSDH (ultimately the pathogenetic cycle is identical, the alternative interpretations differ merely in their starting points). Therefore, there is a clear diagnostic and prognostic potential of hematologic indices and ratios in the setting of cSDH.

Conclusion

Our data indicate that hematological indices bear a diagnostic and prognostic potential in cSDH management and warrant further higher quality and in-depth research. Clinicians should be more vigilant and treat this condition with higher scrutiny than once previously thought. Our results on mortality and recurrence add to this notion, yet at the same time also show that follow-up is inadequate. Croatia needs a national database to appropriately monitor outcomes of neurosurgical procedures.

Authors' Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by H.B., S.K., and W.M., H.B., S.K., and K.B., and H.B., J.M.V., A.D., and G.M., respectively. The first draft of the manuscript was written by H.B. and W.M. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethical Approval

The study was approved by the Institutional Review Board.

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None.

Conflict of Interest

None declared.

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