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A Clinical Decision Support System for Early Recognition of Thrombotic Microangiopathy in Hospitalized Patients

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Research Article

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Abstract

Background

Thrombotic microangiopathy (TMA) is a time-sensitive clinical syndrome in which acute kidney injury, anemia, and thrombocytopenia may be attributed to more common conditions encountered during hospitalization. This overlap can delay recognition and treatment. We evaluated a rule-based clinical decision support system designed to identify laboratory patterns compatible with TMA using routinely available data. We conducted a retrospective, observational, single-center study using hospitalizations recorded at AOU Maggiore della Carità, Novara. The source dataset included 30,816 hospitalizations, of which 16,724 had at least four blood samples. The system generated alerts from serum creatinine, hemoglobin, and platelet values at admission and during hospitalization. An enriched validation cohort was independently reviewed by nephrologists through a dedicated dashboard and classified as no TMA, possible TMA requiring further evaluation, or high-probability TMA. We assessed alert concordance with clinical classification, diagnostic performance, reasons for discordance, in-hospital mortality, and operational workload.

Results

The final validation cohort included 1,394 hospitalizations; 1,076 (77%) generated at least one alert. Expert review classified 839 hospitalizations (60%) as no TMA, 473 (34%) as possible TMA, and 82 (6%) as high-probability TMA. The system alerted 81 of 82 high-probability cases (99%) and 443 of 473 possible cases (94%). When possible and high-probability cases were combined, sensitivity was 94.4%, specificity 34.2%, positive predictive value 48.7%, and accuracy 58.2%. Interestingly, algorithm-assisted review identified 82 high-probability hospitalizations compared with 51 TMA/TTP diagnoses documented in routine care, corresponding to 31 additional cases and a 61% increase in case detection. Finally, in-hospital mortality increased from 14.7% in the no-TMA group to 43.9% in the high-probability group. The system generated a mean of 2.2 alerts per day.

Conclusions

A simple rule-based clinical decision support system using routinely collected laboratory data showed high sensitivity for clinically relevant TMA patterns and identified substantially more high-probability cases than routine diagnostic coding. Its limited specificity supports its use as a first-line surveillance tool followed by expert clinical review, rather than as a standalone diagnostic classifier. Prospective multicenter validation is required to determine whether implementation can reduce diagnostic delay and improve patient outcomes.

Background

Acute kidney injury (AKI) is common among hospitalized patients and is associated with prolonged hospital stay, progression to chronic kidney disease, and increased mortality. Because AKI is a syndrome rather than a single disease, timely identification of its underlying cause is essential. In complex hospital settings, however, potentially treatable etiologies may be obscured by sepsis, surgery, malignancy, bleeding, drug exposure, or pre-existing kidney dysfunction.

Thrombotic microangiopathy (TMA) is characterized by endothelial injury, microvascular thrombosis, microangiopathic hemolytic anemia, thrombocytopenia, and variable organ involvement, with the kidney frequently affected. ‴ Recognition is particularly challenging when the clinical phenotype is incomplete or when laboratory abnormalities are attributed to more prevalent conditions. Diagnostic delay is clinically relevant because several forms of TMA require urgent, etiology-specific treatment, including plasma exchange, complement inhibition, or removal of a precipitating factor.″

Existing diagnostic pathways and disease-specific scores are valuable once TMA is suspected, but they do not continuously screen the broad population of hospitalized patients in whom the diagnosis has not yet been considered. Routine laboratory testing offers a potential opportunity for earlier recognition: changes in serum creatinine, hemoglobin, and platelet count are widely available, longitudinally measured, and collectively reflect major components of the TMA phenotype. An automated system that detects compatible patterns could therefore act as a first-line surveillance layer and prompt focused clinical reassessment.

We developed a rule-based clinical decision support system based on routinely collected laboratory parameters. The present study aimed to evaluate whether this system could identify hospitalized patients with a clinical profile compatible with TMA, quantify its diagnostic performance against nephrologist review, characterize the main causes of discordance, and estimate its potential operational burden in daily hospital practice.

Methods

Study design and data source

This retrospective, observational, single-center study used data from AOU Maggiore della Carità, Novara, Italy, and was approved by the local Ethics Committee within the NOV_AKI study (CE 220/19). The source database contained 30,816 hospitalizations recorded between August 2020 and December 2022. All procedures involving human participants were conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments. A hospitalization was defined as one hospital admission; a sample was defined as one laboratory time point. Multiple samples could be available during the same hospitalization.

Hospitalizations with fewer than four blood samples were excluded, leaving 16,724 hospitalizations for preliminary screening. An enriched subset of 1,736 hospitalizations was assembled for clinical review and included: (1) 1,316 hospitalizations with a simultaneous alert involving serum creatinine,

hemoglobin, and platelets; (2) 51 hospitalizations with a documented diagnosis of TMA or thrombotic thrombocytopenic purpura (TTP); and (3) a random sample of 369 hospitalizations without an alert. The final performance analysis included 1,394 hospitalizations with at least four blood samples and at least one sample containing all three required parameters. The remaining 342 hospitalizations were excluded because of incomplete laboratory data (Table 1).

Table 1
Flow of the study population.

Analytical step	Hospitalizations, n
Overall source database	30,816
Hospitalizations with ≥ 4 samples after preliminary filtering	16,724
Enriched subset submitted to clinical review	1,736
Final subset included in the performance analysis	1,394
Excluded from the clinical subset because of incomplete laboratory data	342

Clinical decision support rules

The system used serum creatinine (sCr), hemoglobin (Hb), and platelet count (PLT) to generate two alert types. An admission alert was triggered by the concurrent presence of sCr > 1.2 mg/dL, PLT < 150 × 10^3/μL, and Hb < 13 g/dL in men or < 12 g/dL in women. A longitudinal alert was triggered during hospitalization by an increase in sCr ≥ 0.3 mg/dL, consistent with the KDIGO stage 1 AKI criterion, or sCr > 1.2 mg/dL, together with a decrease in PLT ≥ 50 × 10^3/μL and a decrease in Hb ≥ 0.5 g/dL within 48 hours.[7] For each hospitalization, the final automated output was binary: at least one alert or no alert. Alerts were further categorized as occurring at admission, during hospitalization, or at both time points.

Clinical review and reference classification

Anonymized hospitalizations in the validation cohort were independently reviewed by two nephrologists using a dedicated dashboard displaying longitudinal laboratory trends. Reviewers independent and blinded to the automated alert status, assigned a score from 0 to 10, where 0 indicated the lowest and 10 the highest clinical probability of TMA, and could enter free-text notes supporting their assessment. Scores were grouped into three prespecified categories: no TMA (0–3), possible TMA requiring further evaluation (4–6), and high-probability TMA (7–10).

Statistical analysis

For performance analyses, possible and high-probability TMA hospitalizations were combined as clinically positive cases, whereas the no-TMA category was considered clinically negative. We calculated sensitivity, specificity, positive predictive value (PPV), and accuracy. Descriptive analyses examined alert timing, reasons for false-positive classification, distribution by hospital department, in-hospital mortality

across clinical categories, and the mean daily alert burden. Because the validation cohort was deliberately enriched for alerted and clinically relevant cases, performance estimates were interpreted within that sampling framework and were not assumed to represent unselected hospital-wide prevalence.

Results

Clinical classification and additional high-probability cases

The final validation cohort comprised 1,394 hospitalizations. At least one automated alert was generated in 1,076 hospitalizations (77%), whereas 318 generated no alert. Following specialist review, 839 hospitalizations (60%) were classified as no TMA, 473 (34%) as possible TMA requiring further evaluation, and 82 (6%) as high-probability TMA (Table 2).

Table 2
Distribution of hospitalizations by clinical class (n = 1,394).

Clinical score	The clinical category	n	%
0–3	No TMA	839	60
4–6	Possible TMA / further evaluation	473	34
7–10	High-probability TMA	82	6
	Total	1,394	100

The clinically most relevant finding was the difference between TMA recognition during routine care and the number of high-probability cases identified after algorithm-supported review. Only 51 hospitalizations had been documented as TMA/TTP in routine clinical records, whereas expert reassessment identified 82 high-probability hospitalizations. Thus, the combined surveillance and review process identified 31 additional high-probability cases, corresponding to a 61% increase in case detection. Of the 82 high-probability hospitalizations, 81 (99%) generated at least one automated alert.

Concordance with clinical review and diagnostic performance

The system generated at least one alert in 81 of 82 high-probability hospitalizations (99%) and in 443 of 473 possible TMA hospitalizations (94%). Alerts were also present in 552 of 839 hospitalizations classified as no TMA (66%), indicating high sensitivity but limited specificity. Among high-probability cases, 32 alerts (40%) were generated only at admission, 41 (50%) only during subsequent sampling, and 8 (10%) at both time points. In the possible TMA group, the corresponding figures were 210 (47%), 194 (44%), and 39 (9%). In the no-TMA group, admission-only alerts accounted for 354 of the alerted cases (64%), whereas 181 (33%) were generated exclusively from longitudinal trends.

When possible, and high-probability TMAs were combined as clinically positive cases, the confusion matrix included 524 true positives, 552 false positives, 31 false negatives, and 287 true negatives

(Table 3). Sensitivity was 94.41%, specificity 34.21%, PPV 48.70%, and accuracy 58.18%.

Table 3
Confusion matrix for the automated alert compared with the combined clinical reference (possible or high-probability TMA versus no TMA).

Automated output	Clinically positive	Clinically negative	Total
Alert	TP = 524	FP = 552	1,076
No alert	FN = 31	TN = 287	318
Total	555	839	1,394

Causes of false-positive alerts

Detailed review of 198 false-positive hospitalizations with longitudinal alerts showed that the most frequently documented explanations were a clinical picture considered non-suggestive of TMA (73 cases, 37%), hemorrhage (33 cases, 17%), and non-significant laboratory fluctuations (reported in the source analysis as 17.9%). Less frequent explanations included malignancy (6 cases, 3%), sepsis (4 cases, 2%), chronic kidney disease (3 cases, 2%), hemodilution (2 cases, 1%), and other conditions (5 cases, 3%). No explanatory note was available in 55 cases (28%). Overall, most false-positive alerts reflected nonspecific or transient changes in routine laboratory values or clinically recognizable alternative diagnoses.

Alert distribution and operational workload

Across 21,703 laboratory samples from the final cohort, the system generated 1,626 alerts: 660 (41%) at the first sample and 966 (59%) during subsequent sampling. Among high-probability hospitalizations with longitudinal alerts, 30% originated from intensive care and 26% from cardiac surgery, consistent with the clinical complexity and high prevalence of competing causes of anemia, thrombocytopenia, and AKI in these settings. Admission alerts originated predominantly from the emergency department.

Over an observation period of 730 days, the system generated an average of 2.2 alerts per day, with a maximum of eight alerts per day. This volume suggests that daily specialist review could be feasible within an organized nephrology consultation pathway.

Clinical outcomes

Interestingly, in-hospital mortality increased progressively with the clinical probability of TMA: 14.66% in the no-TMA group, 23.89% in the possible TMA group, and 43.90% in the high-probability group (Table 4). Ordinary discharge was more frequent in the no-TMA group (52.44%) than in the possible (45.67%) and high-probability (21.95%) groups. Although these outcomes do not establish etiologic confirmation, they support the clinical relevance of the specialist classification and indicate that the alert system preferentially identified patients with greater illness severity.

Table 4
In-hospital outcomes according to clinical TMA probability.

Outcome	High-probability TMA	Possible TMA	No TMA
Death	36 (43.90%)	113 (23.89%)	123 (14.66%)
Ordinary discharge	18 (21.95%)	216 (45.67%)	440 (52.44%)

Discussion

In this study, we evaluated a rule-based clinical decision support system designed to identify laboratory patterns compatible with TMA among hospitalized patients. Three findings have direct clinical relevance. First, the system alerted almost all hospitalizations classified by nephrologists as high-probability or possible TMA. Second, algorithm-supported review identified 31 additional high-probability hospitalizations beyond those documented in routine care, representing a 61% increase in case detection. Third, the mean alert burden was approximately two cases per day, suggesting that the system could be potentially integrated into a daily specialist review workflow without generating an unmanageable volume of notifications.

The principal translational value of the system lies in addressing the period before a formal diagnostic pathway is activated. TMA is not usually missed because confirmatory tests are unavailable but because the syndrome is not considered early enough. In hospitalized patients, AKI, anemia, and thrombocytopenia are common and often have plausible alternative explanations. Sepsis, hemorrhage, malignancy, major surgery, hemodilution, drug exposure, and chronic kidney disease may mimic or coexist with TMA.[3,4]" A surveillance system that continuously examines the joint behavior of these parameters may therefore provide a practical bridge between routinely generated laboratory data and focused clinical assessment.

The 61% increase in high-probability case detection should be interpreted as evidence of improved recognition rather than proof of additional confirmed TMA diagnoses. The reference classification was based on expert nephrologist review, not on systematic etiologic confirmation with peripheral blood smear, lactate dehydrogenase, haptoglobin, ADAMTS13 activity, complement testing, or histology. Nevertheless, the finding that 81 of 82 high-probability cases were alerted indicates that the rule set rarely failed to identify the laboratory phenotype considered clinically relevant. The progressive increase in mortality across the three clinical categories further shows that the review process captured a clinically meaningful gradient of disease severity."

The modest specificity was expected from a first-line screening strategy based on three nonspecific laboratory variables. The system was intentionally designed to favor sensitivity because the clinical cost of overlooking a time-sensitive TMA may exceed the cost of reviewing an alert that is subsequently dismissed. Most false positives were attributable to transient laboratory variation, bleeding, or other readily recognizable clinical conditions. Accordingly, the alert should not be interpreted as a diagnosis.

Its intended function is to trigger a structured second-level assessment, including evaluation of hemolysis markers, blood smear, medication exposure, clinical context, ADAMTS13 activity when indicated, and complement investigations in selected patients.[5,7,10,,]

The distinction between admission and longitudinal alerts may be useful for future refinement. Admission alerts were responsible for many false-positive cases and often reflected prevalent abnormalities without information on temporal evolution. By contrast, alerts based on subsequent changes may better capture an evolving microangiopathic process. Future versions could assign different weights to baseline abnormalities and dynamic trajectories, incorporate additional laboratory variables such as lactate dehydrogenase, bilirubin, haptoglobin, reticulocyte count, and coagulation parameters, and account for competing diagnoses. A deterministic high-sensitivity layer could also be followed by a supervised machine-learning model trained to stratify alerted cases according to the likelihood of clinically relevant TMA.

The enriched validation design was necessary to make detailed manual review feasible, but it affected the interpretation of the performance measures. The cohort included a deliberately high proportion of alert-positive and clinically relevant hospitalizations and therefore does not reproduce the distribution expected in an unselected hospital population. Specificity, PPV, and accuracy calculated in this cohort should not be extrapolated directly to hospital-wide implementation. A prospective study applying the system to all eligible admissions, with prespecified diagnostic testing and blinded outcome adjudication, will be required to estimate real-world predictive values and determine whether alerts shorten the time to specialist assessment or treatment.

This study has additional limitations. It was retrospective and conducted at a single center. The clinical score used as the reference standard has not been externally validated, and information on inter-rater agreement and adjudication was not available in the source dataset. TMA etiology was not systematically confirmed in every high-probability case. The current rule set does not distinguish primary from secondary TMA and may identify patients with severe systemic illness in whom laboratory changes reflect multiple simultaneous mechanisms. Finally, the effect of implementation on diagnostic testing, treatment decisions, kidney outcomes, length of stay, and mortality remains unknown.

Despite these limitations, the results support a pragmatic model of digital surveillance in which automated laboratory screening precedes, but does not replace, expert clinical reasoning. The low daily alert volume makes implementation potentially feasible, while the high sensitivity reduces the likelihood that clinically relevant patterns remain unnoticed. Prospective multicenter validation should now evaluate whether this workflow can reduce diagnostic delay, improve etiologic classification, and facilitate timely initiation of appropriate treatment.

Conclusions

A rule-based clinical decision support system using routinely available serum creatinine, hemoglobin, and platelet data identified nearly all hospitalizations judged clinically compatible with possible or high-probability TMA and increased recognition of high-probability cases compared with routine diagnostic coding. The system should be regarded as an early surveillance tool that prompts specialist review, not as a stand-alone diagnostic test. Its clinical value and effect on patient outcomes require confirmation in a prospective, multicenter implementation study.

Tables

Abbreviations

Abbreviation	Definition
ADAMTS13	A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
AKI	Acute kidney injury
CKD	Chronic kidney disease
FN	False negative
FP	False positive
Hb	Hemoglobin
KDIGO	Kidney Disease: Improving Global Outcomes
PLT	Platelet count
PPV	Positive predictive value
sCr	Serum creatinine
TMA	Thrombotic microangiopathy
TN	True negative
TP	True positive
TTP	Thrombotic thrombocytopenic purpura

Declarations

Ethics approval and consent to participate: The study was approved by the local Ethics Committee within the NOV_AKI study (CE 220/19). The requirement for individual informed consent should be reported according to the approval and applicable regulations.

Consent for publication: Not applicable.

Availability of data and materials: To be completed by the authors in accordance with institutional and data-protection requirements.

Competing interests: Ageing Tech S.r.l. is the applicant and exclusive owner of Italian patent application No. 102026000016600, filed on 9 June 2026, entitled *"Method for the automatic detection of the risk of onset of thrombotic microangiopathy (TMA) in hospitalized patients."* The clinical decision support system evaluated in this study represents an earlier version of the method described in the patent application. Carlo Maria Alfieri, Giuseppe Castellano, Elisa Di Natale, Francesca Martelli, and Massimiliano Roccetti are named inventors on the patent application. All intellectual property, ownership, licensing, and commercialization rights related to the patent are exclusively held by Ageing Tech S.r.l. Authors affiliated with Ageing Tech S.r.l. are employees of the company. The remaining authors declare no competing interests.

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