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“CAROL DAVILA” UNIVERSITY OF MEDICINE AND PHARMACY
BUCHAREST
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Predicting The Clinical Outcome of Sepsis Patients Based on Biological Parameters, Using Big Data Analysis Methods

SUMMARY OF THE DOCTORAL THESIS

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SYNTHESIS OF THE MAIN IDEAS

1. The fundamental problem

Sepsis is defined, according to the Sepsis-3 consensus (2016), as life-threatening organ dysfunction caused by a dysregulated host response to infection. It is one of the leading causes of mortality worldwide: a Global Burden of Disease study estimated, for the year 2017, 48.9 million cases and over 11 million associated deaths, with sepsis involved in approximately 20% of all global deaths. In intensive care units, approximately 30% of patients receive this diagnosis. The burden of the disease is profoundly unevenly distributed: the age-standardized incidence rate ranges from over 1,500 cases per 100,000 inhabitants in Sub-Saharan Africa to under 250 in North America and Western Europe, with Romania at 270 cases per 100,000. However, data from Central and Eastern Europe remain scarce and affected by the imprecision of administrative coding, so that the true magnitude of the phenomenon in Romania is incompletely known.

Early recognition of high-risk patients and the optimal allocation of intensive care resources represent the main avenues for improving prognosis. The classical risk-stratification tools - the SOFA, qSOFA, APACHE II/III/IV, and SAPS II scores - provide a standardized assessment but have important limitations: they were calibrated decades ago, rely on predefined sets of variables, and assume linear relationships, and therefore cannot capture the complex, nonlinear, and time-dependent associations between clinical and laboratory parameters. In parallel, although more than 250 sepsis biomarkers have been studied, their usefulness in reliably predicting survival remains limited, each capturing only an isolated facet of this heterogeneous syndrome.

In this context, Big Data and machine learning methods offer an alternative capable of modeling precisely these nonlinear relationships between variables. Routine laboratory tests, performed daily in every hospital, are abundant, inexpensive, and almost universally available, yet their prognostic value remains largely untapped. The fundamental problem of this thesis is to determine whether the information contained in these routine investigations, exploited through modern analytical methods, can anticipate the outcome of patients with sepsis and can complement the classical risk-assessment tools - a question of particular relevance for resource-limited health systems, where sophisticated investigations are not always available.

2. General part - current state of knowledge

2.1. Sepsis and the limitations of classical prognostic systems

The concept of sepsis has undergone a progressive evolution over the past three decades: from the criteria of the systemic inflammatory response syndrome (Sepsis-1, 1991), refined in 2001 (Sepsis-2) to highlight organ dysfunction in severe sepsis, to the current definition (Sepsis-3, 2016), which abandoned the SIRS-based approach, redefined sepsis as life-threatening organ dysfunction, and introduced the quick SOFA (qSOFA) score for early risk stratification. The chapter synthesizes the epidemiology and clinical impact of the disease, highlighting the global inequality of its burden - age-standardized incidence and mortality rates that are much higher in low- and middle-income countries (the age-standardized mortality rate was 148.1 per 100,000 globally in 2017, with Romania at 54.1) - and confirming, on the basis of the international ICON study, that sepsis remains a major challenge in European intensive care units, including those in Romania.

The limitations of the classical scoring systems (SOFA, APACHE II/III/IV, SAPS II, SSS, OASIS, LODS) are analyzed: developed for the patient populations and care settings of an earlier era, they struggle with both calibration and discrimination in the contemporary care of sepsis, particularly for the prediction of in-hospital mortality. The SOFA score, although widely used because of its simplicity, was developed largely on the basis of expert consensus, and the inability of these systems to capture the complex, nonlinear interactions between clinical variables limits the accuracy of their predictions. Finally, the chapter reviews the prognostic biomarkers (lactate, D-dimers, cytokines, procalcitonin, C-reactive protein, derived ratios, etc.), emphasizing that, despite the large number of identified markers, each captures only one facet of the syndrome, and their predictive accuracy in isolation remains insufficient to guide clinical decisions.

2.2. Machine learning models for outcome prediction in sepsis

Given the complex, multi-organ nature of sepsis and the large volume of data generated in intensive care, machine learning algorithms are particularly well suited to extracting subtle patterns that escape traditional scoring systems or clinical reasoning alone. The chapter presents the conceptual and regulatory framework of Big Data–based medicine: the concept of Big Data and the five “V”s (volume, velocity, variety, veracity, value); real-world data and the intensive care databases (MIMIC-III/IV, eICU-CRD); the European Health Data Space (Regulation EU 2025/327); the Artificial Intelligence Act (EU

2024/1689) and the General Data Protection Regulation (GDPR); as well as the guidance of the Food and Drug Administration (FDA) and of the World Health Organization on the ethics and governance of artificial intelligence in health. Data standardization and interoperability (HL7 FHIR, SNOMED CT, LOINC, the common OMOP data model) are also discussed, as essential conditions for the external validation of models across multiple populations.

The core of the chapter is a systematic review of the literature of the past decade (2014–2024), which identified 19 studies using machine learning models to predict outcomes in sepsis based on routine data. Most (16) were retrospective, and the majority relied on databases from the United States (MIMIC, eICU-CRD); sample sizes ranged from 122 to 21,680 patients (median 3,937), and the number of variables from 7 to 129 (mean 45). Laboratory tests were included in all 19 studies. The most frequent models were random forest (12 studies), logistic regression (11), and gradient boosting methods (10), followed by support vector machines, neural networks, and decision trees; the best-performing model reported was a gradient boosting decision tree, with an area under the curve (AUC) of 0.992. The chapter analyzes the performance metrics, the strategies for handling missing data, and interpretability (SHAP-type methods, used in 10 studies), while highlighting two major limitations of the literature: rare external validation (only 5 of 19 studies, of which only two on patients from another country) and inconsistent reproducibility.

Compared with the conventional methods based on organ dysfunction scores, machine learning models generally provided superior performance, through their ability to exploit the nonlinear relationships between variables. The chapter emphasizes, however, in line with current regulatory frameworks, the principle that these tools must complement, not replace, clinical reasoning - the concept of “augmented intelligence”, in which the clinician remains responsible for the final decision. The relevance of this principle for sepsis is illustrated by the Epic Sepsis Model, a commercial tool implemented in hundreds of American hospitals, which upon external validation achieved an area under the curve of only 0.63 (compared with the 0.76–0.83 initially reported) and missed 67% of the actual sepsis cases, confirming the risk of overreliance on models that have not been validated locally.

3. Working hypothesis and research objectives

The central hypothesis of the research is that routine laboratory tests, collected in current clinical practice and analyzed through Big Data and machine learning methods, contain sufficient prognostic information to allow anticipation of the outcome of patients

with sepsis - in particular in-hospital mortality and discharge status - and can complement the classical risk-assessment tools. From this central hypothesis derive three specific hypotheses, corresponding to the three studies of the thesis: (i) the burden, clinico-demographic profile, and mortality of sepsis in a major Romanian emergency center can be characterized starting from administrative and routine laboratory data; (ii) machine learning models trained on such tests can discriminate between favorable and unfavorable outcomes with clinically useful performance, with a restricted subset of tests concentrating most of the predictive information; (iii) eosinophils, assessed both statically and dynamically, provide independent prognostic information regarding in-hospital mortality.

The general objective of the thesis was the development and evaluation, on a large cohort of patients with sepsis from a major Romanian emergency hospital, of methods for anticipating outcomes based on routine laboratory tests, using Big Data analysis methods. This objective was pursued through three studies designed in a logical sequence, in which each stage follows from the results of the previous one:

- establishing the magnitude and characteristics of the problem at the local and national level - characterizing the epidemiological burden, the clinical profile, and the mortality of sepsis (Study 1);
- the actual testing of the central hypothesis - the development, comparison, and validation of machine learning models that, using exclusively routine tests, demographic data, and comorbidities, anticipate patient outcomes, as well as the identification of the minimal subsets of tests with optimal predictive performance (Study 2);
- deepening the understanding of the prognostic role of eosinophils - a predictor unexpectedly highlighted by the explainability analysis in Study 2 - by evaluating their static and dynamic prognostic value, taking into account concurrent hematological abnormalities (Study 3).

4. General research methodology

The research was based on the data of adult patients with sepsis admitted to the Bucharest University Emergency Hospital - the largest emergency hospital in Romania, with more than 1,000 beds - extracted from the hospital information system for the period 1 January 2007 – 31 December 2024. Patients were identified on the basis of a predefined list of codes from the International Classification of Diseases (ICD-10), recorded as a primary or secondary diagnosis, of a structured search in the free-text fields of the discharge diagnosis, and, in the absence of an explicit code, on the basis of a documented infection

associated with acute organ dysfunction, in accordance with the Sepsis-3 criteria. Of the 12,380 records extracted, after applying the inclusion and exclusion criteria, the overall cohort comprised 12,089 adult patients with sepsis; each of the three studies subsequently used a subset defined according to its objectives and to data availability. The computational component of Study 2 was carried out in collaboration with the National University of Science and Technology Politehnica Bucharest, in an interdisciplinary endeavor at the interface between medicine and data science. Initial data processing was performed in Microsoft Excel, and the statistical analyses in the jamovi software (version 2.7.13), with the significance threshold set at $p < 0.05$ and tests being two-sided. The study received the approval of the ethics committees of the university and of the hospital, the data being fully anonymized and collected retrospectively, which is why individual informed consent was not required.

5. Personal contributions - synthesis of the studies

5.1. Study 1 - The burden of sepsis in a major Romanian emergency center (Chapter 5)

The first study established the magnitude and characteristics of the problem at the local level, through an 18-year retrospective analysis of 12,089 patients with sepsis, out of 913,405 total admissions (overall prevalence 1.32%). The prevalence of sepsis increased steadily and substantially, from 0.26% in 2007 to 2.82% in 2024, the increase reflecting improved recognition and documentation, but also a genuinely growing burden in an aging population. The cohort was characterized by a mean age of 68.7 years, with women being significantly older than men (71.5 versus 66.0 years). Approximately one quarter of patients (24.6%) required mechanical ventilation and 6.6% renal replacement therapy, while 27.5% were surgical cases. The most frequent comorbidities were diabetes (27.2%), pneumonia (20.7%), atherosclerosis (14.1%), chronic kidney disease (14.0%), and cancer (12.9%).

Overall in-hospital mortality was substantial - 53.9% - and significantly higher in women (57.3%) than in men (50.7%); however, after adjustment for age, sex, surgical intervention, and comorbidities, men showed slightly higher odds of death (adjusted OR 1.13). Thirty-day mortality, calculated in the subgroup with known vital status, reached 85.1%. Mortality was significantly lower in surgical cases (37.5% versus 60.1%) and increased progressively with age, exceeding 66% in patients older than 80 years; patients who required both mechanical ventilation and renal replacement therapy had the highest

mortality rate (78.0%). In the multivariate analysis, pneumonia (adjusted OR 2.43) and cirrhosis (adjusted OR 2.32) were the strongest independent predictors of mortality, followed by chronic kidney disease, chronic obstructive pulmonary disease, and cancer, whereas diabetes had a marginal, slightly protective effect (OR 0.90). Microbiological data from a subgroup of 2,410 patients showed a predominance of Gram-negative organisms (Escherichia coli, Klebsiella), and the mortality of patients with confirmed COVID-19 was 60.2%.

Compared with international data, the reported mortality significantly exceeds the values of the ICON study (35.3%) and those of Western Europe and North America, approaching those observed in resource-limited health systems. The discussion links this difference to the challenges of the Romanian health system - the low density of intensive care beds, delays in the recognition of sepsis, and the limitations of antimicrobial stewardship programs. The study provides one of the largest datasets on sepsis in Romania and furnished the large, well-characterized cohort on which the subsequent predictive analyses were founded.

5.2. Study 2 - Anticipating outcomes through explainable machine learning models (Chapter 6)

Starting from this cohort, the second study tested the central hypothesis of the thesis. The dataset comprised approximately 600 types of laboratory investigations, from which a set of 50 relevant tests was constructed; to handle data incompleteness, subsets corresponding to the most frequent 10, 20, 30, 40, and 50 investigations were tested, evaluating the trade-off between feature richness and cohort coverage. The laboratory parameters were aggregated as the mean value over the duration of hospitalization - a choice that makes the models perform a retrospective risk stratification at the level of the entire episode, rather than a real-time prediction. The ICD-10 codes were grouped into 14 comorbidity categories. Five algorithms (logistic regression, Support Vector Classifier, random forest, gradient boosting, and Histogram-based Gradient Boosting) were developed and compared, both individually and through four ensemble strategies (Voting, Stacking, Bagging, AdaBoost), for three clinically relevant binary classification scenarios: deceased versus discharged alive, deceased versus cured, and cured versus improved.

The Histogram-based Gradient Boosting model provided the best performance in all scenarios. The highest predictive value of the entire study was obtained for the deceased-versus-cured task (AUC of 0.983 and accuracy of 0.93), followed by the scenario with the

greatest direct clinical relevance - the prediction of survival (deceased versus discharged alive), with an AUC of 0.920 and an accuracy of 0.843 - while the more subtle differentiation between complete recovery and partial improvement reached an AUC of 0.865. The inclusion of comorbidity information consistently improved performance, and a restricted subset of frequently performed tests was sufficient for clinically useful predictive capacity - an important argument for applicability in hospitals with limited resources. The performance obtained compares favorably with that previously reported on the MIMIC and eICU-CRD databases (0.94–0.96).

The explainability analysis (the SHAP method) revealed a coherent core of predictors, common to the three tasks: respiratory, cardiovascular, and neurological comorbidities, urea values, age, platelet count, as well as a series of hematological parameters - leukocytes, lymphocytes, monocytes, and, consistently, eosinophils - alongside markers of hepatic function and cardiac injury (AST, CK-MB). Although the eosinophil percentage was only the 26th most frequently performed test in the dataset, it proved to be one of the strongest predictors in all experiments, a low percentage being inversely associated with a fatal outcome. To our knowledge, this is the first machine learning–based study on outcome prediction in sepsis carried out on a cohort from an Eastern European country, and the observation regarding eosinophils - an accessible predictor, yet absent from the classical scores - directly motivated the third study.

5.3. Study 3 - Static and dynamic eosinophil measures and in-hospital mortality (Chapter 7)

The third study deepened the understanding of the prognostic value of eosinophils, in a cohort of 3,932 patients with sepsis (2021–2024), assessing both static measures (at admission and at the eosinophil nadir) and early dynamics (the trajectory at 48 and 72 hours), through landmark analyses intended to mitigate survivorship and immortal-time bias. Although the static eosinophil count was significantly lower in patients who died, it was not independently associated with in-hospital mortality after adjustment for disease severity and concurrent hematological abnormalities. By contrast, the dynamic behavior of eosinophils had independent prognostic value: a decrease in the eosinophil count at 72 hours was associated with a significantly higher risk of death (OR 1.43), and the persistence of undetectable values was associated with the highest mortality (OR 1.85 at 48 hours and 2.41 at 72 hours); at 48 hours, the signal did not reach statistical significance, which underscores the importance of the timing of assessment.

Notably, pancytopenia at the eosinophil nadir - present in 18.2% of patients - remained independently associated with mortality, emphasizing that eosinopenia must be interpreted within the broader context of multilineage hematological dysfunction. The chapter integrates these observations with the biological mechanisms of eosinophils - active participants in the host's antiviral and antibacterial defense - and with the mechanisms of eosinopenia in acute infection (apoptosis induced by endogenous corticosteroids, catecholamines, and cytokines, tissue margination, and bone-marrow retention). The results support the interpretation of eosinopenia as an indicator of systemic immune dysregulation, rather than an isolated prognostic biomarker, and contribute to reconciling previously contradictory results in the literature, highlighting the time-dependent nature of eosinophil behavior in sepsis.

6. Conclusions and personal contributions

Taken together, the three studies confirm the central hypothesis of the thesis: routine laboratory tests, collected in current clinical practice and exploited through Big Data and machine learning methods, contain sufficient prognostic information to anticipate the outcome of patients with sepsis and can complement the classical risk-assessment tools. This approach is of particular value in resource-limited health systems, in which sophisticated investigations are not always available, whereas routine tests are almost universally accessible. The main original contributions, measurable and identifiable in the personal-contributions part, are as follows:

- the first comprehensive characterization, over 18 years and 12,089 patients, of the epidemiological burden and mortality of sepsis in a major Romanian emergency center, with the identification of the independent predictors of mortality in the Romanian context (Chapter 5);
- the development of the first machine learning models for outcome prediction in patients with sepsis in Romania, using exclusively routine laboratory tests and achieving top performance (AUC of 0.983) (Chapter 6);
- the demonstration that a restricted subset of frequently performed tests retains a high predictive capacity, which makes the approach applicable in resource-limited hospitals (Chapter 6);
- the identification, through explainability analysis (SHAP), of eosinophils as a consistent and important predictor of outcome, although absent from the classical severity scores (Chapter 6);

- the conduct of the first study to evaluate both the static measures and the early dynamics of eosinophils through landmark analyses, demonstrating that the trajectory - and not the static value - is independently associated with mortality (Chapter 7);
- the dissemination of the results through three scientific papers published in extenso in ISI-indexed journals.
- a contribution to the geographic and contextual diversity of a field dominated by models developed on established databases (such as MIMIC) or on small cohorts, demonstrating that prediction models must be evaluated in the concrete context in which they are to be applied (Chapters 5 and 6);
- the demonstration that eosinopenia must be interpreted within the broader context of multilineage hematological dysfunction, with pancytopenia at the eosinophil nadir being independently associated with mortality (Chapter 7);
- the proposal of a unified methodological framework, based on routine laboratory tests - accessible and low-cost - and on Big Data analysis methods, applicable across diverse hospital settings, and which contributes to reconciling contradictory results in the literature regarding the role of eosinophils in sepsis (Chapters 6 and 7);

Beyond technical performance, the developed models must be understood for what they are - a support for clinical decision-making, not a replacement for it. The dominant concept is that of “augmented intelligence”: artificial intelligence remains a “decision-making copilot”, in which the final decision belongs to the physician, who integrates the algorithm's output into clinical judgment and into the context of the multidisciplinary team. An important consequence of this perspective is the redefinition of the evaluation criteria: the ultimate criterion of an artificial intelligence tool is not the algorithm's area under the curve, but the patient - the real clinical and operational outcomes, such as time to intervention, complications avoided, missed cases, and the correctness of triage, being those that can justify the introduction of a model into clinical practice.

The transition from performance demonstrated on a dataset to use in real clinical decision-making requires the fulfillment of minimal safety conditions - data transparency, external and local validation, post-implementation monitoring, and continuous governance - since a model's performance can degrade over time, with changes in laboratory protocols, patient demographics, or clinical guidelines. The fact that the first study of the thesis revealed a mortality different from that reported in other regions confirms precisely that models cannot be adopted uncritically from other contexts but must be validated locally. On the basis of these considerations, the directions for continuing the research aim at developing models sensitive to the temporal dimension, capable of early, real-time prediction, their prospective and multicenter validation, their integration into the clinical workflow alongside established scores such as SOFA, the confirmation of the prognostic value of eosinophil dynamics through formal tests of incremental performance, as well as the development of a national, anonymized, and standardized clinical database dedicated to sepsis.

Last but not least, the entire structure of retrospective research on large patient cohorts depends on a fundamental condition - the accuracy of the primary data. Unlike prospective studies, retrospective ones cannot correct the recording errors that occur at the time of care, but can only inherit the quality of the existing data. The rigor of each physician in coding diagnoses and in accurately recording procedures and clinical course thus becomes the foundation on which subsequent medical knowledge is built, and the present thesis represents both an exploitation of existing data and an argument for a culture of rigor in medical documentation.

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