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Original Article

Vitamin D at hospital admission as an independent predictor of outcome of sepsis patients: Results of a secondary analysis from a "Need-Speed" trial prospective cohort

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ABSTRACT

Background: Early prognostic stratification of septic patients at hospital admission is challenging, especially in the elderly. Considering the well-known immunomodulatory effects of vitamin D and its common deficiency among elderly, we aimed to evaluate if vitamin D plasma levels (25(OH)D) at hospital admission could be a prognostic biomarker in septic patients.

Methods: Secondary analysis of data and samples from the multicenter Need-Speed trial, a multicenter study involving the emergency and internal medicine wards of five Italian hospitals. 1132 consecutive patients admitted to hospital with suspected sepsis were enrolled. 859 were confirmed to have sepsis at the end of the diagnostic work-up and 829 patients were included in the analysis. 25(OH)D at admission was measured using an automated chemiluminescence assay.

Results: Among the 829 patients included (median age 81 years [IQR: 72–87]), severe hypovitaminosis D was observed (median 11.2 ng/mL [IQR: 8.0–19.4]). At univariate analysis, baseline 25(OH)D levels were significantly lower in patients who died at 30 and 90 days and higher among patients discharged alive within 15 days ($p < 0.05$). Multivariate models confirmed 25(OH)D as an independent predictor of 90-day mortality and of discharge alive at 15 days ($p < 0.05$). Moreover, a 25(OH)D threshold of 12 ng/mL independently predicted both survival at 90 days (OR: 0.5961 [0.4068–0.8735]) and discharge alive at 15 days (OR: 1.6055 [1.1738–2.1960]).

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Conclusions: Lower 25(OH)D levels were independently associated with poorer clinical outcomes in older patients with sepsis. Therefore, hypovitaminosis D assessment may provide prognostic value beyond validated risk stratification tools, warranting prospective validation.

1. Introduction

Sepsis is currently defined as a life-threatening organ dysfunction caused by a dysregulated host response to an infection, according to the Sepsis-3 consensus [1].

The incidence of this condition is still increasing, and the mortality rate remains unacceptably high (20–36%), especially in the elderly. Furthermore, sepsis displays a hard impact on both healthcare and economic systems worldwide, as it is characterized by long-term effects, going beyond the acute phase of the disease, that strongly impact survivors' quality of life [2–6]. Sepsis accounts globally for >48 million incident cases and >10 million deaths every year; therefore, it has been declared a worldwide health concern by the World Health Organization (WHO).

According to the prevailing view among clinicians and researchers, sepsis is characterised by a dysregulated immune response to infection that results in organ dysfunction, the progression of which is influenced by both the causative pathogen and host factors as the degree of immune activation during the early phases, followed by immune exhaustion, tolerance mechanisms, and vascular dysregulation (e.g. endothelial glycocalyx shedding and overactivation of the complement system). As this disruption of the homeostasis appears to be dynamic, recent progresses in sepsis molecular characterization led to the identification of several endotypes, differing in terms of pathogens, infection site and comorbidities, as well as of different subphenotypes among patients, each one characterized by specific genetic and metabolomic profiles, and leukocyte populations [7,8].

Ageing is a well-recognized risk factors associated with increased mortality in patients with sepsis, particularly in high-income countries [3,6]. Sepsis-related mortality follows a triphasic pattern, characterised by early and late in-hospital peaks and a third peak, typical of older adults, emerging between 60 and 90 days and persisting for years after the onset of sepsis. This pattern is likely driven by the higher prevalence in this population of predisposing factors, such as comorbidities and malnutrition, which contribute to a chronic, persistent low-grade systemic inflammatory state [9,10].

The age-related physiological decline of the immune system, along with associated immune dysregulation, represents an important contributor to the increased incidence of sepsis in older adults [9,10]. Furthermore, age-related immunological alterations pose an additional challenge for the timely identification of sepsis, as clinical presentations in older adults often differ from those observed in younger patients [9]. Consequently, commonly used clinical scores such as qSOFA or NEWS2 may demonstrate limited sensitivity in this frail population [11].

Vitamin D is an essential nutrient with a well-recognized immunomodulatory role [12–14], and its metabolism is frequently altered in older adults. Hypovitaminosis D is highly prevalent in this population [15–17], thereby contributing to frailty [16,18,19]. Accordingly, it is conceivable that reduced plasma vitamin D levels may influence the progression of sepsis toward adverse outcomes by modulating pro-inflammatory responses (e.g. cytokine release, oxidative stress, and lymphocyte activation) and impairing endothelial integrity [12], particularly in older individuals In this context, vitamin D deficiency may serve not only as a biomarker of frailty but also as a surrogate for immune reserve, potentially useful for early patient stratification.

The aim of this study is to investigate the role of vitamin D plasmatic levels as a prognostic biomarker in septic patients referring to the emergency department by performing a secondary analysis of the data and samples collected during the multicenter "Need-Speed" trial [20].

2. Materials and methods

2.1. Patients

Need-Speed trial was a multicenter observational study whose design, methods and main results have been already published [20]. This trial, developed between 2013 and 2015, involved five Italian Emergency Departments and Internal Medicine wards, where consecutive adult patients were enrolled according to the already described inclusion and exclusion criteria. Accordingly, patient enrolment and diagnostic classification were originally based on the Sepsis-2 criteria, which represented the accepted clinical definition at that time. The original study was approved by the local ethical committee of all the recruiting sites and was designed and conducted according to the principles of the Declaration of Helsinki, as previously described [20. The study design of this secondary analysis is reported in Fig. 1.

2.2. Endpoints definition

The aim of the study was to investigate the relationship between plasma vitamin D levels (evaluated in terms of 25(OH)D) and sepsis outcome through the following endpoints: i) 7-days mortality; ii) 30-days mortality; iii) 90-days mortality; iv) proportion of discharge alive within 15 days from admission.

2.3. Data collection

Every patient fulfilling the inclusion criteria and agreeing to be enrolled in the study was asked to date and sign an informed consent form within 24h from hospital admission. Demographic, clinical, and laboratory data were collected prospectively and stored in a dedicated database. Relevant data obtained from the medical records were used to calculate the most relevant clinical indices used in the present study (Charlson Comorbidity Index - CCI, National Early Warning Score 2 - NEWS2). The essential data for the endpoints' evaluation were collected by reaching by phone each participant during the follow-up, to verify if the patient was still alive or, in case of death, to record the date of the event [21].

2.4. Sample collection

Within 24h from hospital admission, each patient underwent a blood draw for routine clinical analyses as well as to collect biological material for research purposes. Routine hematological evaluations performed in clinical practice were assured by the relevant facilities of the recruiting sites. Blood samples collected for research purposes were immediately processed and stored at −80 °C until analysis.

2.5. Vitamin D evaluation

Plasma vitamin D levels were measured as 25(OH)D using a commercial assay validated for clinical use. Baseline plasma samples were sent to the clinical biochemistry facility of "Maggiore della Carità" university hospital (Novara, Italy) and assessed by chemiluminescence using the LIAISON 25 OH vitamin D total assay kit, following the manufacturer's instructions.

2.6. Statistical analysis

Data extracted from the study database and vitamin D

quantifications were analyzed by univariate and multivariate models to assess their statistical significance toward the expected endpoints. Measures of central tendency and dispersion, expressed as median and interquartile range (IQR), were used to investigate continuous variables, while categorical variables were expressed as frequencies (percentages). Statistical comparisons were based on the appropriate test based on the nature of the variable under investigation (Mann-Whitney U test for continuous variables and Pearson χ^2 test for categorical variables). The statistically significant data obtained in the univariate analysis were used to build stepwise multivariate logistic regression models, model calibration was assessed with the Hosmer–Lemeshow goodness-of-fit test. Odds ratio (OR) were expressed in terms of 95% confidence interval (CI). Receiver-operating characteristic (ROC) curves were used to evaluate the clinical significance of the proposed cut-off. The threshold to identify the statistically significant results was set at 0.05 (two-tailed). Statistical evaluations were performed using the software package Statistica for Windows (release 12, TIBCO software Inc., Palo Alto, CA, USA) or MedCalc® statistical software (version 22.018, MedCalc Software Ltd., Ostend, Belgium).

3. Results

This study is a secondary analysis of the samples and data collected during the Need Speed trial: the study population was represented by 829 elderly patients, with a slight prevalence of the male gender (440 males vs 389 females). The complete demographic, clinical, and laboratory features of the patients included in the study are reported in Table 1.

As only patients with a confirmed infection were included in the study population (Fig. 1), the primary site of infection leading to sepsis development was investigated. Pneumonia was the most common cause of sepsis, being identified as the leading cause in 461 patients (55.6%). The other primary sites of infection identified were the urinary tract in 128 patients (15.4%), the abdomen in 98 patients (11.8%), the soft tissues in 57 patients (6.9%), and other or multiple sites in 85 patients (10.3%).

A univariate analysis has been used to evaluate the relationship between baseline plasma vitamin D levels and the previously described endpoints. As shown in Table 2, at univariate analysis, baseline plasma vitamin D was significantly lower in patients who died at 30 and 90 days while it was significantly higher among patients discharged alive from hospital within 15 days from admission ($p < 0.05$).

Since baseline plasma vitamin D showed a statistically significant correlation with late mortality (at 30 and 90 days) as well as with the probability of being discharged alive within 15 days from admission, these parameters were evaluated together with other demographic, clinical and laboratory evidence to identify possible confounding factors. The results of the univariate analyses for these endpoints are shown in supplementary Tables 1–3.

Table 1
Study population characteristics. Data are expressed as median and interquartile range (IQR).

	Median	IQR
Age (years)	81	72–87
Clinical scores		
Glasgow Coma Scale	15	15–15
NEWS2	5	3–7
Charlson Comorbidity Index	3	1–4
Vital parameters		
Temperature (°C)	37.7	36.6–38.2
Heart rate (beats/min)	100	90–110
Respiratory rate (breaths/min)	24	20–28
Systolic pressure (mm Hg)	120	110–135
Diastolic pressure (mm Hg)	70	60–80
Arterial blood gas analysis		
pH	7.4	7.4–7.5
pO_2 (mm Hg)	69.7	59.1–82.2
pCO_2 (mm Hg)	34.2	30.0–39.7
HCO^{3-} (mEq/L)	23.7	21.1–26.1
SaO_2 (%)	94.8	92.0–96.6
Lactate (mmol/L)	1.4	1.0–2.0
Laboratory findings		
Hemoglobin (g/dL)	12.2	10.8–13.4
Leukocytes (cells × 10^3/mm^3)	13	9.4–17.1
Platelets (cells × 10^3/mm^3)	222	158–301
Creatinine (mg/dL)	1.1	0.8–1.7
CRP (mg/L)	103.3	36.7–184.6
Potassium (mEq/L)	4.0	3.6–4.4
Sodium (mEq/L)	137.0	133.0–139.0
Glycemia (mg/dL)	131.0	109.0–167.0
Procalcitonin (ng/mL)	0.6	0.2–4.5
Vitamin D (ng/mL)	11.2	8.0–19.4

Abbreviations: NEWS2 = National Early Warning Score 2, CRP = C-reactive protein.

Once identified the demographic, clinical and laboratory variables showing a statistically significant correlation with the proposed endpoints, the independent association between vitamin D levels and late mortality (at 30 and 90 days) as well as discharge within 15 days from admission, was investigated using different stepwise logistic regression models, which results are shown in supplementary Tables 4–8.

When considering mortality at 30 days (supplementary Table 4), vitamin D was not confirmed as a reliable predictor.

When evaluating the predictors of late mortality at 90 days, multivariable analysis confirmed an independent association between vitamin D levels and the investigated outcomes considering

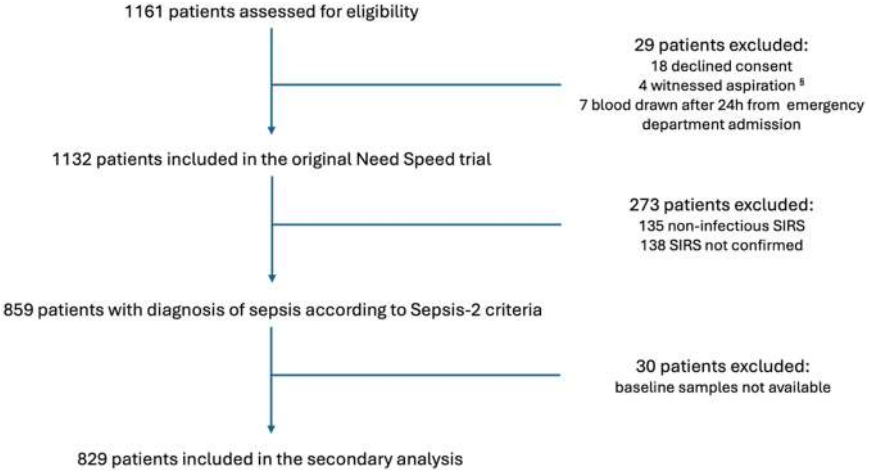

Fig. 1. Study design. § Witnessed aspiration is intended as aspiration of food or oral content observed by a relative or caregiver.

Table 2
Univariate analysis of baseline plasma vitamin D relationship with study endpoints. For each category, the number of valid entries has been indicated (n). Bold indicates statistically significant values.

Endpoint	Patients not reaching the endpoint			Patients reaching the endpoint			Z	p-value
	n	Median (ng/mL)	IQR	n	Median (ng/mL)	IQR		
7-days mortality	745	11.2	8.0–19.4	84	11.1	8.0–18.8	0.4628	0.7447
30-days mortality	661	11.4	8.0–20.0	168	10.3	8.0–17.2	2.3051	**0.0212**
90-days mortality	592	12.0	8.0–20.5	237	9.6	8.0–16.4	3.5618	**0.0004**
Discharged alive within 15 days	473	10.5	8–17.2	356	12.5	8.2–21.3	−3.5467	**0.0004**

demographic data, clinical scores and laboratory variables identified in the univariate model (supplementary Table 5).

Similarly, when assessing predictors of discharge within 15 days from hospital admission, multivariable analysis confirmed an independent association between vitamin D levels and the investigated outcomes taking in consideration demographic data, clinical scores and laboratory variables identified in the univariate model (supplementary Table 6).

To search for a cut-off for vitamin D in predicting 90 days mortality and discharge within 15 days from admission, ROC curves were built (supplementary figure 1 and 2). As shown in supplementary figure 1, a vitamin D level lower than 12 ng/mL showed a 64.98% (IQR: 58.5–71.0) sensitivity and a 49.32% specificity (IQR: 45.2–53.4) in predicting mortality at 90 days, with a positive likelihood ratio of 1.28 (Area under the Curve –AUC- 0.579, $p < 0.001$) . On the contrary, a plasma vitamin D level higher than 12 ng/mL showed a 51.40% (IQR: 46.1–56.7) sensitivity and a 59.41% specificity (IQR: 54.8–63.9) in predicting the discharge alive within 15 days from hospital admission, with a positive likelihood ratio of 1.27 (Area under the Curve –AUC- 0.572, $p < 0.001$) (supplementary figure 2).

To further explore the potential clinical relevance of vitamin D levels association with late mortality in clinical practice, the previous multivariate models have been recalculated also using a vitamin D cut-off of 12 ng/mL (supplementary Table 7 and 8 and Fig. 2 and 3).

4. Discussion

Sepsis management still represents a difficult clinical challenge, especially in the elderly, a frail population in which the physiological decline in immune system functions further increase the disease-associated mortality rate [9,10]. Moreover, ageing is associated with an increased incidence of hypovitaminosis D, due to a reduction in sun exposure, nutritional intake, and intestinal absorption of this essential vitamin [15–17]. On the other hand, Vitamin D modulates innate and adaptive immune responses, as well as endothelial barrier integrity [12–14,22].

According to these considerations, the aim of this study was to investigate the prognostic value of plasma vitamin D levels in predicting mortality and/or discharge alive within 15 days from hospital admission in patients diagnosed with sepsis.

The Need Speed study cohort consisted of elderly patients (median age: 81, IQR: 72–87) admitted to hospital wards with suspected sepsis or septic shock. Although the inclusion criteria for the original study were based on the Sepsis-2 definition, the study protocol required that a definitive diagnosis was assigned at the end of the diagnostic workup, distinguishing between non-infectious SIRS, clinically documented sepsis, and microbiologically documented sepsis [20]. This secondary analysis was performed after excluding patients with non-infectious SIRS; therefore, only patients with confirmed sepsis were considered. As expected, plasma vitamin D levels (median: 11.2 ng/mL, IQR: 8.0–19.4) were found to be well below the sufficiency threshold, thus contributing to the frailty of this population [16,18,19]. Other general considerations, emerging from the analyzed data, concern the origin of sepsis and the mortality trend over time. Indeed, sepsis origin has been identified in pneumonia in more than half of the patients (55.6%), while mortality increased during follow-up from 84 deaths at 7 days to 237 at 90 days, highlighting the continued increase in mortality after discharge as a significant problem for the elderly. The apparently moderate clinical parameters at admission may depend on to the atypical presentation of sepsis in elderly patients and the early-phase enrolment design aimed at capturing patients at first contact in the Emergency Department.

It is noteworthy that lower plasma vitamin D levels at admission were associated to higher mortality at 30 and 90 days and to a lower probability of discharge alive within 15 days from admission. Vitamin D baseline plasma value retained its predictive value toward 90-days mortality and discharge within 15 days from admission after the correction for demographics, clinical severity and comorbidity indexes and laboratory parameters used in clinical practice. It should be pointed out that the AUROC value of 0.579 indicates that vitamin D has limited standalone discriminative performance, however, this does not preclude its role as an independent prognostic contributor in multivariable models. Therefore, the value of vitamin D lies in providing additional

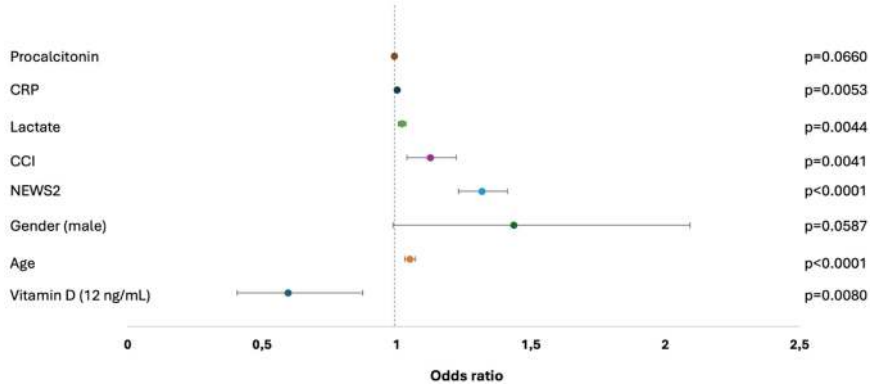

Fig. 2. Forest plot predicting mortality. Stepwise logistic regression of demographic, clinical and laboratory predictors of late mortality (90 days) considering a vitamin D level ≥ 12 ng/mL. The variables entered in the model are shown in the figure. Leukocyte count, hemoglobin, platelet count, potassium, sodium, and creatinine did not enter in the model.

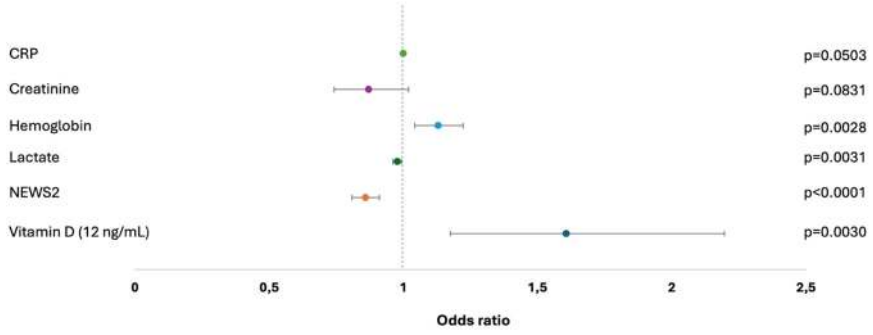

Fig. 3. Forest plot predicting discharge alive. Stepwise logistic regression of demographic, clinical and laboratory predictors of discharge alive within 15 days from hospital admission considering a vitamin D cut-off of 12 ng/mL. The variables entered in the model are shown in the figure. Charlson comorbidity index, age, male gender, leukocyte count, potassium, and procalcitonin did not enter in the model.

independent prognostic informations that enhance stratification when used in combination with established clinical scores.

This observation could be explained by the well-recognized immunomodulatory role of vitamin D, since immune responses appear to be strongly altered not only during acute sepsis, but also later, after the acute phase conclusion.

A strong amount of evidence demonstrate the regulatory role of vitamin D in the inflammatory process allowing to balance inflammation and tissue injury: vitamin D inhibits the production of pro-inflammatory cytokines (IL-2, IL-6, IL-8, TNF-alpha) and increases the production of anti-inflammatory ones such as IL-10 [23,24]. Vitamin D also increases the efficacy of the immune system, stimulating the production of antimicrobial molecules (cathelicidin, beta-defensin), nitric oxide synthase (NOS) and IL-1 [25]. These effects regulate both innate and adaptive immune responses involved in inflammation [26–28] and are all mediated by the activation of vitamin D receptor (VDR) that is expressed, in a vitamin D-dependent amount, in several types of immune cells (monocytes, macrophages, T cells, B cells) [29]. The regulatory effects of vitamin D appear to be more relevant to the adaptive than to the innate immune response, which may explain our finding that vitamin D levels do not seem to influence the early presentation of sepsis. Indeed, we found no differences in terms of clinical severity or organ dysfunction at hospital admission between patients with and without severe vitamin D deficiency. Moreover, vitamin D was not associated with 7-day mortality, in line with previous findings [30]

For a long time, it was hypothesized that late mortality in sepsis depended solely on patients' comorbidities. In 1997, Quartin and coworkers observed that the risk of mortality remained elevated even after resolution of the acute phase of disease in patients with sepsis compared with those with a similar comorbidity burden [31]. Since this observation, understanding of sepsis pathophysiology has steadily advanced, and it is now well recognized that, while early mortality (7- and 30-days) appears to be primarily related to sepsis severity and comorbidity burden, patients who survive the acute phase may still develop the so-called persistent inflammation, immunosuppression and catabolism syndrome (PICS). PICS is a clinical condition characterised by a self-perpetuating cycle of ongoing organ dysfunction, inflammation, and catabolism, ultimately resulting in sarcopenia, immunosuppression, metabolic alterations and changes in bone marrow function. Therefore, our results suggest that a better baseline vitamin D status may be associated with a lower probability of this late and severe complication of sepsis, potentially through the attenuation of persistent inflammation and the prevention of PICS [32–34].

Consistently, a better vitamin D baseline status may be a surrogate indicator of the patient's immune system conditions. Therefore, higher circulating vitamin D concentrations may contribute to a better-regulated immune response, potentially improving patients' ability to counteract the dysfunctional inflammatory response typically observed in sepsis. In fact, by reducing the release of pro-inflammatory mediators (e.g. cytokines and oxidative stress) while enhancing anti-inflammatory responses, promoting lymphocyte and macrophage activation, and improving endothelial barrier integrity, higher plasma vitamin D level may actively support a faster restoration of homeostasis at both the immune and tissue level.

Beyond these mechanistic aspects, it should also be considered that higher circulating vitamin D levels could simply identify patients with greater exposure to sunlight and therefore more self-sufficient behavior, with better nutritional intake and absorption and, possibly, healthier gut microbiota. However, in our cohort, vitamin D levels maintained their prognostic value even after adjusting for comorbidity burden, suggesting that, beyond this indirect association, vitamin D may play an independent immunological role in favoring rapid recovery and discharge from hospital and reducing mortality.

Starting from these findings, it could be postulated that the administration of vitamin D in patients with sepsis might improve their outcomes; although randomized controlled trials testing vitamin D supplementation in critically ill patients (e.g., the VITdAL-ICU and the PETAL network trial) have produced conflicting results, these studies were not designed specifically for elderly septic patients, a subgroup in whom targeted interventions might be more effective [35]. Future studies should evaluate whether correcting vitamin D deficiency during hospitalization alters the trajectory of immune recovery, reduces PICS, and improves long-term outcomes in elderly septic patients.

Our study is characterized by both limitations and strengths. Among the limitations, the most relevant relates to the study design: this is a secondary analysis of patients prospectively enrolled in a previous trial [20], and the endpoints considered here were not pre-specified in the original study protocol. Moreover, as patients were enrolled in the original study, the inclusion criteria were based on the Sepsis-2 definition currently accepted at the time of Need Speed trial, as the actual Sepsis-3 definition was published only in 2016 therefore, the present findings may not be fully generalisable to contemporary cohorts classified exclusively according to Sepsis-3 definitions [1]. However, the impact of this limitation on the validity of our findings is mitigated by the fact that the final diagnosis was established through a rigorous process of dual independent physician review, which substantially enhanced the diagnostic specificity of the Sepsis-2 criteria. Moreover, although Sepsis-3 generally identifies a subgroup with greater illness severity and mortality risk, comparative literature suggests a considerable overlap between Sepsis-2 and Sepsis-3 populations in elderly Internal Medicine cohorts [5]. In addition, the observed mortality pattern and distribution of infection sources in our cohort are consistent with contemporary sepsis epidemiology [10]. Again, considering the study design, its observational nature could account for some residual confounders even after the corrections applied for multivariate analyses. As the clinical data were already collected during a study conducted in the 2013–2015 timeframe, it was not possible to retrieve information about patients' nutritional and functional status, frailty indices as well as

chronic treatment and use of vitamin D supplements, which could have influenced vitamin D measurements. In addition, although the cohort was enrolled between 2013 and 2015, the prevalence of hypovitaminosis D in older adults has remained consistently high in subsequent years [15,16], supporting the continued relevance of our observations. However, we acknowledge that changes in sepsis definitions, clinical management, and supportive care over time may limit the applicability of these findings to current clinical practice. Vitamin D levels were evaluated only at the time of hospital admission, so it was not possible to evaluate the kinetics of vitamin D levels modifications during hospitalization. Nevertheless, considering that the whole study population presented, regardless to the outcomes, with a marked hypovitaminosis, it is reasonable to suppose that very few of the enrolled patient was undergoing an active vitamin D supplementation at the time of hospital admission. Finally, the vitamin D assay was not associated with parathyroid hormone measurement, possibly leading to a further underestimate of hypovitaminosis D in a condition of systemic inflammation as described for other systemic inflammatory syndromes [36,37].

On the other hand, the study also has some relevant strengths. First, its prospective design allowed data collection during a prolonged follow-up of 90 days. Moreover, it is multicentric: the involvement of 5 different hospitals not only granted a large population cohort but also resulted in an increased representativeness of the general population. Lastly, all samples were analyzed at the same time and with the same methodology, thus assuring uniformity in both conservation and manipulation, finally resulting in a lower analytical variability and in a higher comparability of the obtained results.

5. Conclusions

These data, derived from a secondary analysis of the Need Speed trial, highlight the value of assessing plasma vitamin D at the time of emergency department admission as an independent predictor of disease evolution. More in detail, at hospital admission, lower vitamin D levels were independently associated to late mortality (at 90 days), while higher vitamin D levels to discharge within 15 days from hospital admission. A cut-off value of 12 ng/mL appeared to be reliable for both outcomes. Although this proposed threshold has been tested only within our study cohort and requires validation in independent datasets, our findings support the clinical utility of measuring plasma vitamin D concentration in elderly patients with sepsis as a biomarker of frailty. The exploratory cutoff of 12 ng/mL may provide clinicians with an early warning signal to identify high-risk frail patients requiring closer monitoring, a more aggressive therapeutic approach, nutritional assessment, and more intensive care, including admission to the intensive or intermediate care unit, if appropriate. Furthermore, our results suggest the need for closer post-discharge follow-up in order to prevent, or enable early treatment, of late harmful complications related to the acute condition itself or to hospitalization.

Therefore, we suggest using vitamin D not as a stand-alone biomarker, but in addition and in combination with other currently used clinical scores to better stratify patient risk and disease evolution.

Considering that, as observed in this cohort, even small differences in baseline vitamin D levels within a context of severe hypovitaminosis appear to be associated with clinical outcomes, it is conceivable that well-designed interventional clinical trials could evaluate the effectiveness of vitamin D supplementation in improving sepsis outcomes in elderly patients with sepsis. This is particularly relevant given that current evidence on vitamin D_3 supplementation in critically ill patients remains controversial and is not specifically tailored to the elderly population [35].

Authors contributions

PPS and MR contributed equally to the paper. PPS, MR, and LC drafted the manuscript. PPS, LC and GCA contributed to study conceptualization and design. PPS and LC performed data analyses. ST, FV, MP (Marco Primatesta), PAT, RR and UD performed or supervised vitamin D evaluations. EL, SDS, MLM, GB, FF, GCA and LC coordinated clinical data collection. MP (Mario Pirisi) revised clinical data and contributed to data curation. All authors reviewed the draft. All authors read and approved the final version of the manuscript.

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Declaration of competing interest

The authors declare that they have no competing interests

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2026.107025.

Data availability

Data will be made available from the copatesponding author (pierpaolo.sainaghi@med.uniupo.it) upon reasonable request

References

[1] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA, J Am Med Assoc 2016;315:801. https://doi.org/10.1001/jama.2016.0287.

[2] He RR, Yue GL, Dong ML, Wang JQ, Cheng C. Sepsis biomarkers: advancements and clinical applications-A narrative review. Int J Mol Sci 2024;25:9010. https://doi.org/10.3390/ijms25169010.

[3] La Via L, Sangiorgio G, Stefani S, Marino A, Nunnari G, Cocuzza S, La Mantia I, Cacopardo B, Stracquadanio S, Spampinato S, Lavalle S, Maniaci A. The global burden of sepsis and septic shock. Epidemiol (Basel) 2024;5:456–78. https://doi.org/10.3390/epidemiologia5030032.

[4] Guarino M, Perna B, Cesaro AE, Maritati M, Spampinato MD, Contini C, De GR. 2023 update on sepsis and septic shock in adult patients: management in the emergency department. J Clin Med 2023;12:3188. https://doi.org/10.3390/jcm12093188.

[5] Ibarz M, Haas LEM, Ceccato A, Artigas A. The critically ill older patient with sepsis: a narrative review. Ann Intensive Care 2024;14:6.

[6] Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, Colombara DV, Ikuta KS, Kissoon N, Finfer S, Fleischmann-Struzek C, Machado FR, Reinhart KK, Rowan K, Seymour CW, Watson RS, West TE, Marinho F, Hay SI, Lozano R, Lopez AD, Angus DC, Murray CJL, Naghavi M. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the global burden of disease study. Lancet 2020;395:200–11. https://doi.org/10.1016/S0140-6736(19)32989-71.

[7] Gerard R, Dewitte A, Gross F, Pradeu T, Lemoine M, Goret J, Mamani-Matsuda M. Is "pre-sepsis" the new sepsis? A narrative review. PLoS Pathog 2025;21:e1013372. https://doi.org/10.1371/journal.ppat.1013372.

[8] Meyer NJ, Prescott HC. Sepsis and septic shock. N Engl J Med 2024;391:2133–46. https://doi.org/10.1056/NEJMra2403213. and catabolism syndrome. Crit Care Clin. 2017; 33: 245-258. 10.1016/j.ccc.2016.12.001.

[9] Alhamyani AH, Alamri MS, Aljuaid NW, Aloubthani AH, Alzahrani S, Alghamdi AA, Lajdam AS, Alamoudi H, Alamoudi AA, Albulushi AM, AlQarni SN. Sepsis in aging populations: a review of risk factors, diagnosis, and management. Cureus 2024;16:e74973. https://doi.org/10.7759/cureus.74973.

[10] Ramoni D, Tirandi A, Montecucco F, Liberale L. Sepsis in elderly patients: the role of neutrophils in pathophysiology and therapy. Intern Emerg Med 2024;19:901–17. https://doi.org/10.1007/s11739-023-03515-1.

[11] Oczkowski S, Alshamsi F, Belley-Cote E, Centofanti JE, Hylander Møller M, Nunnaly ME, Alhazzani W. Surviving sepsis campaign guidelines 2021: highlights for the practicing clinician. Pol Arch Intern Med 2022;132:16290. https://doi.org/10.20452/pamw.16290.

[12] Rizzi M, Sainaghi PP. Vitamin D: a nutraceutical supplement at the crossroad between respiratory infections and COVID-19. Int J Mol Sci 2025;26:2550. https://doi.org/10.3390/ijms26062550.

[13] Wimalawansa SJ. Infections and autoimmunity-the immune system and vitamin D: a systematic review. Nutrients 2023;15:3842. https://doi.org/10.3390/nu15173842.

[14] Ao T, Kikuta J, Ishii M. The effects of vitamin D on immune system and inflammatory diseases. Biomolecules 2021;11:1624. https://doi.org/10.3390/biom11111624.

[15] Giustina A, Bouillon R, Dawson-Hughes B, Ebeling PR, Lazaretti-Castro M, Lips P, Marcocci C, Bilezikian JP. Vitamin D in the older population: a consensus statement. Endocrine 2023;79:31–44. https://doi.org/10.1007/s12020-022-03208-3.

[16] Marcos-Pérez D, Sánchez-Flores M, Proietti S, Bonassi S, Costa S, Teixeira JP, Fernández-Tajes J, Pásaro E, Valdiglesias V, Laffon B. Low vitamin D levels and frailty status in older adults: a systematic review and meta-analysis. Nutrients 2020;12:2286. https://doi.org/10.3390/nu12082286.

[17] Mosekilde L. Vitamin D and the elderly. Clin Endocrinol (Oxf) 2005;62:265–81. https://doi.org/10.1111/j.1365-2265.2005.02226.x.

[18] Zheng Z, Xu W, Wang F, Qiu Y, Xue Q. Association between vitamin D3 levels and frailty in the elderly: a large sample cross-sectional study. Front Nutr 2022;9:980908. https://doi.org/10.3389/fnut.2022.980908.

[19] Ju SY, Lee JY, Kim DH. Low 25-hydroxyvitamin D levels and the risk of frailty syndrome: a systematic review and dose-response meta-analysis. BMC Geriatr 2018;18:206. https://doi.org/10.1186/s12877-018-0904-2.

[20] Mearelli F, Fiotti N, Giansante C, Casarsa C, Orso D, De Helmersen M, Altamura N, Ruscio M, Castello LM, Colonetti E, Marino R, Barbati G, Bregnocchi A, Ronco C, Lupia E, Montrucchio G, Muiesan ML, Di Somma S, Avanzi GC, Biolo G. Derivation and validation of a biomarker-based clinical algorithm to rule out sepsis from noninfectious systemic inflammatory response syndrome at emergency department admission: a multicenter prospective study. Crit Care Med 2018;46:1421–9. https://doi.org/10.1097/CCM.0000000000003206.

[21] Castello LM, Gavelli F, Baldrighi M, Salmi L, Mearelli F, Fiotti N, Patrucco F, Bellan M, Sainaghi PP, Ronzoni G, Di Somma S, Lupia E, Muiesan ML, Biolo G, Avanzi GC. Hypernatremia and moderate-to-severe hyponatremia are independent predictors of mortality in septic patients at emergency department presentation: a sub-group analysis of the need-speed trial. Eur J Intern Med 2021;83:21–7. https://doi.org/10.1016/j.ejim.2020.10.003.

[22] Rizzi M, Avellis V, Messina A, Germano C, Tavella E, Dodaro V, Vitale R, Revelli A, Zola P, Picone S, Paolillo PM, Mondì V, Masturzo B, Manzoni P, Sainaghi PP. Vitamin D supplementation in neonatal and infant MIS-C following COVID-19 infection. Int J Mol Sci 2024;25:3712. https://doi.org/10.3390/ijms25073712.

[23] Zhang Y, Leung DY, Richers BN, Liu Y, Remigio LK, Riches DW, Goleva E. Vitamin D inhibits monocyte/macrophage proinflammatory cytokine production by targeting MAPK phosphatase-1. J Immunol 2012;188:2127–35. https://doi.org/10.4049/jimmunol.1102412.

[24] Adams JS, Hewison M. Unexpected actions of vitamin D: new perspectives on the regulation of innate and adaptive immunity. Nat Clin Pract Endocrinol Metab 2008;4:80–90. https://doi.org/10.1038/ncpendmet0716.

[25] Pinheiro da Silva F, Machado MC. Antimicrobial peptides: clinical relevance and therapeutic implications. Peptides 2012;36:308–14. https://doi.org/10.1016/j.peptides.2012.05.014.

[26] Bellan M, Andreoli L, Mele C, Sainaghi PP, Rigamonti C, Piantoni S, De Benedittis C, Aimaretti G, Pirisi M, Marzullo P. Pathophysiological role and therapeutic implications of vitamin D in autoimmunity: focus on chronic autoimmune diseases. Nutrients 2020;12:789. https://doi.org/10.3390/nu12030789.

[27] Bishop E, Ismailova A, Dimeloe S, Hewison M, White JH. Vitamin D and immune regulation: antibacterial, antiviral, anti-inflammatory. JBMR Plus 2021;5:e10405. https://doi.org/10.1002/jbm4.10405.

[28] Martens PJ, Gysemans C, Verstuyf A, Mathieu AC. Vitamin D's effect on immune function. Nutrients 2020;12:1248. https://doi.org/10.3390/nu12051248.

[29] Sadeghi K, Wessner B, Laggner U, Ploder M, Tamandl D, Friedl J, Zügel U, Steinmeyer A, Pollak A, Roth E, Boltz-Nitulescu G, Spittler A. Vitamin D3 down-regulates monocyte TLR expression and triggers hyporesponsiveness to pathogen-associated molecular patterns. Eur J Immunol 2006;36:361–70. https://doi.org/10.1002/eji.200425995.

[30] Seok H, Kim J, Choi WS, Park DW. Effects of vitamin D deficiency on sepsis. Nutrients 2023;15:4309. https://doi.org/10.3390/nu15204309.

[31] Quartin AA, Schein RM, Kett DH, Peduzzi PN. Magnitude and duration of the effect of sepsis on survival. Department of veterans affairs systemic sepsis cooperative studies group. JAMA, J Am Med Assoc 1997;277:1058.

[32] Mira JC, Gentile LF, Mathias BJ, Efron PA, Brakenridge SC, Mohr AM, Moore FA, Moldawer LL. Sepsis pathophysiology, chronic critical illness, and persistent inflammation-immunosuppression and catabolism syndrome. Crit Care Med 2017;45:253–62. https://doi.org/10.1097/CCM.0000000000002074.

[33] Mira JC, Brakenridge SC, Moldawer LL, Moore FA. Persistent inflammation, immunosuppression and Catabolism Syndrome. Crit Care Clin 2017;33:245–58.

[34] Chadda KR, Puthucheary Z. Persistent inflammation, immunosuppression, and catabolism syndrome (PICS): a review of definitions, potential therapies, and research priorities. Br J Anaesth 2024;132:507–18. https://doi.org/10.1016/j.bja.2023.11.052.

[35] National Heart, Lung, and Blood Institute PETAL Clinical Trials Network, Ginde AA, Brower RG, Caterino JM, Finck L, Banner-Goodspeed VM, Grissom CK, Hayden D, Hough CL, Hyzy RC, Khan A, Levitt JE, Park PK, Ringwood N, Rivers EP, Self WH, Shapiro NI, Thompson BT, Yealy DM, Talmor D. Early high-dose vitamin D3 for critically ill, vitamin D-deficient patients. N Engl J Med 2019;381:2529–40. https://doi.org/10.1056/NEJMoa1911124.

[36] Sainaghi PP, Bellan M, Nerviani A, Sola D, Molinari R, Cerutti C, Pirisi M. Superiority of a high loading dose of cholecalciferol to correct hypovitaminosis d in patients with inflammatory/autoimmune rheumatic diseases. J Rheumatol 2013;40:166–72. https://doi.org/10.3899/jrheum.120536.

[37] Sainaghi PP, Bellan M, Antonini G, Bellomo G, Pirisi M. Unsuppressed parathyroid hormone in patients with autoimmune/inflammatory rheumatic diseases: implications for vitamin D supplementation. Rheumatol (Oxf) 2011;50:2290–6. https://doi.org/10.1093/rheumatology/ker314.