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MEDS score and vitamin D status are independent predictors of mortality in a cohort of Internal Medicine patients with microbiological identified sepsis

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Abstract. – OBJECTIVE: Sepsis is a life-threatening disease resulting from the interaction between pathogen and host response; its dysregulation causes organ dysfunction, high morbidity, and mortality. Despite the increase of septic patients admitted to Internal Medicine wards, data about clinical predictors of mortality in this setting are still lacking. The aim of this study was to evaluate the role of MEDS score and vitamin D as predictors of mortality (28-day and 90-day) in septic patients admitted to the Internal Medicine department.

PATIENT S AND METHODS: Prospectively collected clinical data, lab tests including vitamin D, and clinical scores (SIRS, MEDS, SCS, REMS, SOFA, qSOFA) were retrospectively analyzed. Eighty-eight microbiologically identified septic patients (median age 75 years old, IQR 65-82 years old; range 37-94 years old) were evaluated.

RESULTS: Twenty-three patients (26.1%) died at 28 days, 33 (37.5%) died at 90 days. The logistic regression showed a positive effect of MEDS score (p=0.006; OR 1.24, 95% CI 1.08-1.49), and a negative effect of low vitamin D levels (p=0.008, OR 0.83, 95% CI 0.72-0.94) on mortality. Moreover, the cut-off of 7 points for MEDS score and of 7 ng/ml for vitamin D levels significantly predicted poor prognosis at 28 and 90 days.

CONCLUSIONS: MEDS score and vitamin D levels represent independent predictors of mortality in a cohort of Internal Medicine septic patients. Further studies on larger samples are needed to confirm our results and to clarify the pathophysiological mechanisms at the basis of vitamin D deficiency as a predictor of mortality in septic patients.

Key Words
Sepsis, Internal medicine, MEDS, Vitamin D, SOFA, qSOFA.

Introduction

Sepsis is one of the deadliest diseases of all times. It represents one of the major burdens of the healthcare system and it is responsible for mil-

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lions of "preventable" deaths every year, worldwide[1]. Basing on the data from hospital-treated sepsis in high-income countries, it accounts for 30 million episodes and 6 million deaths per year[1,2]. It has been estimated that sepsis causes or contributes to approximately half of all deaths occurring in hospitals, representing the most expensive condition treated in the US hospitals[3,4]. According to the World Health Assembly, the prevention, diagnosis, and treatment of sepsis should be considered a global health priority[1].

Although most of our knowledge about sepsis is derived from the Intensive Care Unit (ICU) patients, the majority of patients at risk for developing this syndrome are commonly admitted to non-ICU wards[5-9]. The mortality rates are still high, and there is a lack of literature data on this population. In other words, the data about patients who could develop sepsis and how they should be treated are lacking from locations (non-ICU wards) where sepsis is thought to be more common and associated with the poorest outcomes (non-ICU wards)[10]. However, the Internists' interest for sepsis has constantly grown during the last years, and a generalized need for knowledge has been shown[11-14]. The clinical prognostic scores (i.e., SOFA) commonly used in the routine clinical practice have been usually developed in ICU and/or in Emergency Departments (ED) and have not been extensively validated in the Internal Medicine (IM) setting[13,15]. Among those tested, only a few showed good reliabilities to predict mortality[16]. However, their performance was poor and inadequate for elderlies, given the burden of comorbidities influencing their prognosis. At present, there is uncertainty about the clinical score to use for Internal Medicine septic patients.

In the last decade, "nonclassical" effects of vitamin D, such as immunomodulation, have been emphasized besides its role on calcium and bone homeostasis. In particular, vitamin D seems to be able to regulate innate and adaptive immunity[17]. Moreover, an association between the low levels of vitamin D and high-risk of sepsis, including poor sepsis-related outcomes (e.g., mortality, length of hospitalization), have been observed in critically ill patients, although study results are still heterogeneous[18-21]. The greater susceptibility to infections among patients with vitamin D deficiency could be explained, at least in part, by the reduced expression of vitamin-D-dependent antimicrobial peptides (e.g., cathelicidin and defensin)[22]. Currently, the only interventional trial (VITdAL-ICU)[23] aiming to demonstrate a reduction of hospital length of stay in critically ill septic patients by vitamin D supplementation did not reach the primary outcome. However, reduced in-hospital mortality among severely deficient patients was observed[23]. Other interventional trials are still ongoing (e.g., VITDALIZE, VIOLET)[24-25]. As a matter of fact, ICU septic patients show a high prevalence of vitamin D deficiency[19,20]. To the best of our knowledge, only one study evaluated and indicated the vitamin D deficiency among Internal Medicine septic patients[26].

The present study evaluated the role of MEDS score and vitamin D levels as predictors of mortality in a cohort of patients affected by microbiological identified bloodstream infections, admitted to the Internal Medicine Department.

Patients and Methods

Patients

An active surveillance program for sepsis was conducted from January 2014 to December 2014 between two Internal Medicine Inpatient Units (75 total inpatient beds) of the "Agostino Gemelli" University Hospital, Catholic University of Rome, Italy. The surveillance was conducted by the Internal Medicine Sepsis Study Group. According to this program, every patient, for whom the managing physician had requested blood cultures, was evaluated (screening phase). Thus, a total of 226 patients were consecutively screened. The screening program consisted in the collection of clinical data (gender, age, body mass index, vital signs, mental status, risk factors for infection, risk factors for multidrug-resistant infection, co-morbidities), clinical scores [Systemic Inflammatory Response Syndrome (SIRS); Mortality in the Emergency Department Sepsis (MEDS); Simple Clinical Score (SCS); Rapid Emergency Medicine Score (REMS); Sequential Organ Failure Assessment (SOFA, see further)], and laboratory results (blood tests, blood gas analysis, C-reactive protein, procalcitonin, lactates). The vitamin D levels, β-D-glucan, and galactomannan were also recorded. The diagnosis of sepsis was based on Sepsis-2 definition[27]. The evaluation of qSOFA was retrospectively performed, according to SEPSIS-3 definition[28]. The inclusion criteria were: both diagnosis of sepsis and positivity of blood cultures for clinically significant pathogens. The exclusion criteria were: the absence of one of the two inclusion criteria

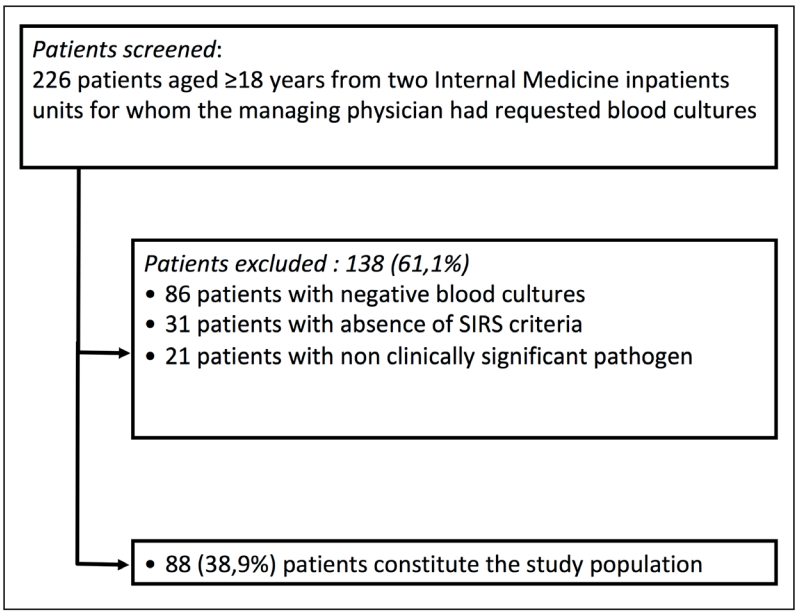

Figure 1. The number of patients evaluated for study inclusion, the number of patients excluded from the study with relative reason, the number of patients included in the study.

or blood culture positivity for contaminant microorganisms (e.g., *coagulase-negative staphylococci, propionibacterium, corynebacterium, micrococcus*). In this last case, an agreement between the managing physician and the Infectious Diseases consultant was obtained. Among 226 screened patients, 138 (61.1%) have been excluded for the reasons showed in Figure 1. Thus, a total of 88 microbiologically-identified septic patients (38.9% of the screened sample) were evaluated for the study. All patients received an empirical antibiotic treatment, subsequently de-escalated on the basis of blood cultures and/or Infectious Diseases consultation, as decided by the managing physician.

Methods

The data prospectively acquired from medical records were retrospectively reviewed to collect the data of microbiologically-identified septic patients at admission, at 48 h and 7 days from admission. The information on 28-day and 90-day mortality was acquired from medical records or by telephone contact. The study was conducted in accordance with the local Ethic Committee dispositions. Given the observational, non-interventional design, the informed consent was waived. The vital signs included systolic, diastolic and mean blood pressure, pulse rate, oxygen saturation, respiratory rate, body temperature, diuresis, and fluid balance. The mental status was assessed by the Glasgow Coma Scale (GCS)[29]. The body mass index was calculated as the body mass divided by the square of the body height (kg/m^2)[30]. Age > 65 years old, immunosuppression, diabetes, surgery in the previous 6 months, active neoplasms, implanted devices (i.e., urinary catheter, central venous catheter, heart valves, and pacemaker) were considered as risk factors for infection[5,7,8]. Moreover, immunosuppression, antibiotic treatment in the previous 6 months, MDR infection in the previous 6 months, hemodialysis, recent hospitalization or residing in long term facilities were considered as risk factors for MDR infection[5]. MEDS is a clinical prediction rule for the mortality rate in patients undergoing blood cultures in the ED, where it was validated[31]. It stratifies patients according to the risk of death by considering 9 items (terminal disease, respiratory difficulty, septic shock, low platelets count, bands > 5%, age > 65 years old, low respiratory tract infection, nursing home resident, altered mental status) and attributing them a score. The total score ranges from 0 to 27. Patients scoring ≤ 4 are classified as "very low-risk" (1.1% of mortality according to the validation study), those scoring 5-7 are classified as "low-risk" (4.4% mortality). A score ranging of 8-12 is considered "moderate risk" (9.3% mortality), the range 13-15 corresponds to "high-risk" (16.1% mortality), while scores > 15 are considered as "very high-risk" (39% mortality). SCS represents a score to predict mortality, validated among patients affected by acute medical diseases[32]. It considers sixteen items predictors of 30-days mortality (age, blood pressure, heart rate, temperature, oxygen saturation, respiratory rate, abnormal ECG, breathless on presentation,

diabetes, coma without intoxication, altered mental status, new stroke on presentation, inability to stand unaided, and pre-existing bedridden status). The total score ranges from 0 to 41. Patients scoring < 4 are classified as "very low-risk" (0.1% of mortality according to the original study), those scoring 4-5 are classified as "low-risk" (1.5% mortality), those scoring 6-7 are considered at "average risk" (3.9% mortality). The range 8-11 corresponds to "high-risk" (10.3% mortality), while scores ≥12 are considered as "very high-risk" (34.4% mortality). According to the validation study, SCS's curve for 30-day mortality showed an AUC of 0.85-0.9. REMS represents a score developed to predict in-hospital mortality among patients admitted to ED for non-surgical diseases[33]. It considers mean arterial pressure, heart rate, respiratory rate, peripheral oxygen saturation, Glasgow Coma Scale score, and age. The total score ranges from 0 to 26. The highest scores predict the highest mortality rate. The AUC for predicting in-hospital mortality is 0.85. SOFA was developed in the 90s by the European Society of Intensive Care Medicine to assess the severity of organ dysfunction associated with sepsis[34]. It considers six organ functions (e.g., respiration, coagulation, liver, cardiovascular, central nervous system, renal) and attributes to each one a score from 1 to 4, where 1 represents low dysfunction and 4 represents severe dysfunction. At present, SOFA has the best performance among other scores to predict in-hospital mortality among ICU patients and its use is recommended by SEPSIS-3 guidelines[35]. The qSOFA represents a new and simple, score to predict the risk of infection and mortality of patients outside ICU[35]. This score is based on 3 clinical variables (e.g., respiratory rate ≥ 22, systolic blood pressure ≤ 100 mmHg and altered mental status) and it does not use any laboratory test result. The qSOFA showed a high predictivity, particularly when applied to patients treated outside ICU. However, the Sepsis-3 task force is explicitly stating the need for the validation of a new score using non-US databases of patients, and a study conducted on a Greek cohort of patients failed to show a high sensitivity of qSOFA for the early prediction of mortality outside ICU[15]. The vitamin D assay was performed as part of the routine laboratory examinations for septic patients. We considered the vitamin D levels suggested by the Endocrine Society guidelines (vitamin D deficiency: 25(OH)D ≤ 19.9 ng/mL; vitamin D insufficiency: 20-29.9 ng/mL; vitamin D normal group: ≥ 30 ng/mL)[36]. A subgroup < 7 ng/ml, with severe deficiency, was also identified.

Statistical Analysis

Several statistical procedures were applied for the analysis of data, both descriptive and inferential, whose results are reported throughout the paper. The ultimate goal of the analysis was to determine which predictors, among the initial set of 34 candidate predictors, affect 28-day and 90-day mortality in a logistic regression framework, respectively. Due to a large number of candidates, a two-stage analysis strategy was first adopted to find few predictors to be eventually used in the logistic regression. At the first stage, a very preliminary screening was done by performing an individual significance test for each candidate predictor. In particular, each numerical variable out of 20 was tested through a two-sample Wilcoxon test, aiming at assessing mean differences between the group of deceased *vs.* that of non-deceased patients. On the other hand, a standard Chi-square test of independence in a two-way contingency table was used for testing the influence of each of the 14 categorical variables on mortality. In both cases, the variables with related p-values < 0.20 were retained for the second stage of the analysis strategy, where a stepwise logistic regression was run for selecting a definite few numbers of predictors; the BIC criterion was used for the application of the stepwise procedure. This two-stage strategy was repeated for both 28-day and 90-day mortality. Afterward, the predictors previously selected were included in a logistic regression model for an in-depth study on their effect at 28-day and 90-day mortality, respectively. For the correct application of logistic regression, the standard model checking techniques were run to assess the model adequacy and thus to validate the analysis method. To supplement logistic regression, an additional ROC curve analysis was done to compare the predictive ability of the relevant predictors. All the computations were carried out by using the free software R[36].

Results

The main clinical characteristics of the evaluated sample are summarized in Table I. A total of 46 patients (52.3%) showed criteria for severe sepsis and 26 (29.5%) for septic shock. Among the 88 enrolled patients, 51 (57.9%) were male, with a 75 years old median age (IR 65-82 years old, range 37-94 years old). Three patients (3.4%) have been transferred to ICU. The median BMI

was 24.59 kg/m^2. A total of 36 patients (40.9%) were immunosuppressed, 32 (35.9%) were diabetic, 35 (39.3%) were affected by neoplasms, 62 (70.4%) had received an antibiotic treatment in the previous 6 months, and 14 (15.9%) had had an MDR infection in the previous 6 months. A total of 66 (75%) patients were carriers of a vescical or central venous catheter. Finally, 21 patients (23.9%) were affected by an end-stage illness. The median systolic pressure was 83 mmHg (IR 73-90, range 51-115), the mean lactate level was 2.02±2 mmol/l, the median PCT 2.79 ng/ml (IR 0.7-19.2, range 0-100), the median SCS 10.39 (IR 6-13, 63% classified as high or very high-risk), the mean SOFA 10.3+/-4.6, the mean MEDS 10.12±4.4, REMS 7.47±3.1, the mean qSOFA 1.02±0.9. The gram-negative bacteria represented the 47.1% of sepsis, the gram-positive accounted for 44.6%, while the fungi were 8.3% of the total. The vitamin D levels were available for 77 out of 88 patients. A total of 75 (97.4%) patients showed insufficient vitamin D levels (< 30 ng/ml), while 44 of them (57.1%) showed a severe vitamin D deficiency (< 7 ng/ml). A total of 23 patients (26.1%) did not survive beyond day 28, while 33 of them (37.5%) did not survive beyond day 90 from the admission.

28-Day Mortality

At the first stage of our two-stage analysis strategy, the results from the two-sample Wilcoxon tests and the Chi-square tests of independence showed that the predictors to be retained for the subsequent stepwise logistic regression were: low BMI (p=0.08), low urine output (p=0.09), age (p=0.06), MEDS (p=0.0001), pO2/FiO2 (p=0.001), qSOFA (p=0.001), REMS (p=0.11), SCS (p=0.007), low vitamin D levels (p=0.11), antibiotic treatment during the prior 6 months (p=0.037), MDR infection during the prior 6 months (p=0.02), end-stage disease (p=0.001), parenteral nutrition (p=0.05), SCS's risk (p=0.033). Lactates (p=0.66), procalcitonin (p=0.77), SOFA at T0 (p=0.25) and SOFA at T2 (p=0.72) did not show any influence on 28-day mortality, thus they were excluded from the next analyses. At the second stage of the analysis, the stepwise logistic regression led to MEDS score and low vitamin D levels as the important predictors of 28-day mortality. Then, the logistic regression in these two predictors showed a positive effect of MEDS score (p=0.003; OR 1.30, 95% CI 1.11-1.61), and a negative effect of low vitamin D levels (p=0.099, OR 0.87, 95% CI 0.73-0.99). Figure 2 displays the ROC curves of MEDS score and the vitamin D levels for 28-day mortality. The AUC of MEDS score was 0.77 (95% CI 0.65 to 0.88), while the AUC of low vitamin D levels was 0.61 (95% CI 0.47 to 0.75); their comparison seems to suggest a better predictive ability of MEDS score with respect to low vitamin D levels (p=0.08). This conclusion is in agreement with the results of the previous logistic regression, where the evidence of the importance of MEDS score (p=0.003) was much stronger than that of low vitamin D levels (p=0.09).

90-Day Mortality

The preliminary screening for 90-day mortality, by means of two-sample Wilcoxon tests and Chi-square tests of independence, pointed to the following predictors to be used in the next stepwise regression: positive fluids balance (p=0.02), low urine output (p=0.06), age (p=0.03), MEDS (p=0.0003), pO2/FiO2 (p=0.009), qSOFA (p=0.01), SCS (p=0.002), SOFA T0 (p=0.18), low vitamin D levels (p=0.007), MDR infection during the prior 6 months (p=0.10), end-stage disease (p=0.008), parenteral nutrition (p=0.17), SCS's risk class (p=0.004). REMS (p=0.50), BMI (p=0.44), lactates (p=0.42), procalcitonin (p=0.23) and SOFA at T2 (p=0.88) did not show any significant influence on 90-day mortality, thus they were excluded from the next analyses.

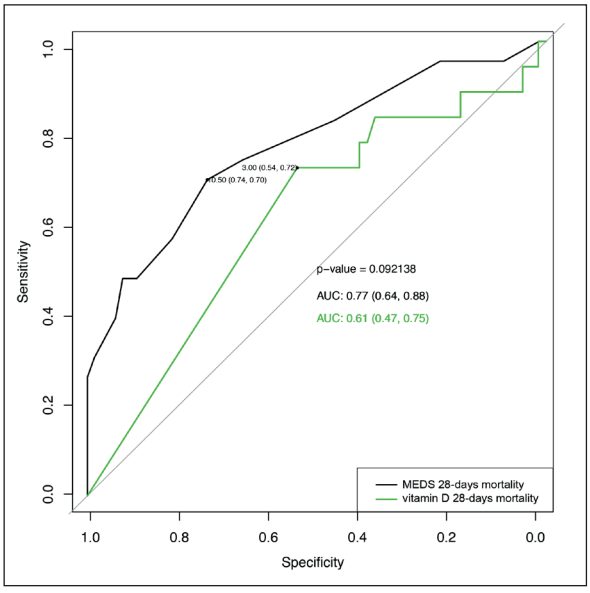

Figure 2. The ROC curves of MEDS score and vitamin D levels for 28-days mortality.

Table I Clinical characteristics of the 88 evaluated patients expressed as median (IQR; range). Median values of patients survived or deceased at 28-days and 90-days and statistical comparison.

	Study patients	Survived at 28-days (65)	Deceased at 28-days (23)	*p*-value	Survived at 90-day (55)	Deceased at 90-day (33)	*p*-value
Male sex	51 (57.9%)	-	-	-	-	-	-
Age (years)	75 (65-82; 37-94)	73	81	0.068	72	80	0.032
BMI	24.59 (22.0-27.5; 17-43)	25.2	23.3	0.087	24.9	24.3	0.440
pO2/FiO2	362.9 (289-399; 101-450)	380.0	314.2	0.001	381.9	323.8	0.009
Lactate	1.5 (1.1-2.2; 0.1-8.8)	1.50	1.55	0.662	1.5	1.6	0.429
Procalcitonin (ng/ml)	2.79 (0.7-19.2; 0.1-100)	3.00	2.63	0.772	4.03	2.43	0.232
Vitamin D (ng/ml)	<7 (<7-9.4; <7-55.7)	7	4.29	0.115	7.7	3.4	0.007
SCS T0	10 (6-13; 2-23)	10	12	0.007	9	12	0.002
SOFA T0	6 (5-7; 0-12)	6	6	0.258	6	6	0.184
MEDS T0	9 (8-12; 2-24)	9	12	<0.001	9	11	<0.001
REMS T0	8 (5.7-9; 0-18)	7	8	0.112	8	8	0.503
qSOFA	1 (0-2; 0-3)	1	2	0.001	1	1	0.016

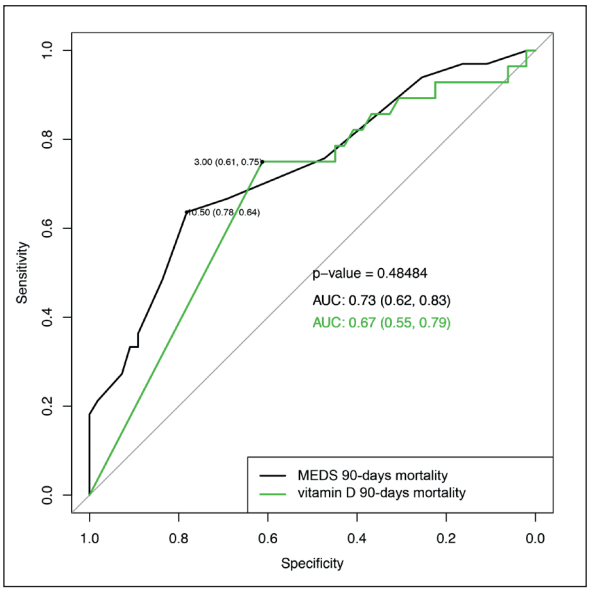

Figure 3. The ROC curves of MEDS score and vitamin D levels for 90-days mortality.

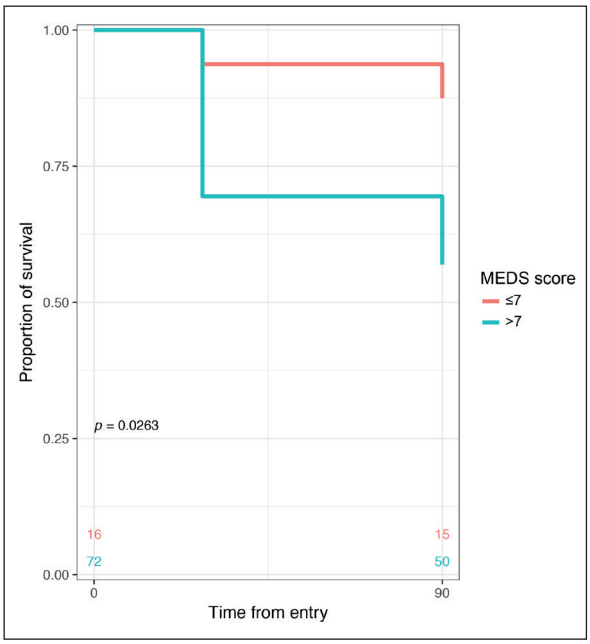

Figure 4. The Kaplan-Meyer curves for differences in survival proportion according to modified MEDS categories.

The stepwise logistic regression still indicated the MEDS score and low vitamin D levels as the important predictors. Then, the logistic regression in these two predictors showed a positive effect of MEDS score (p=0.006; OR 1.24, 95% CI 1.08-1.49), and a negative effect of low vitamin D levels (p=0.008, OR 0.83, 95% CI 0.72-0.94).

Figure 3 displays the ROC curves of MEDS score and vitamin D levels for 90-day mortality. The AUC of MEDS score was 0.73 (95% CI 0.61 to 0.83), while the AUC of low vitamin D levels was 0.67 (95% CI 0.56 to 0.78); their comparison nearly indicates the same predictive ability of the two predictors (p=0.48). This conclusion is still in agreement with the results of the previous logistic regression, where p-values of MEDS score (p=0.006) and low vitamin D levels (p=0.008) were in a quite close accordance.

Table II shows 28-day and 90-day mortality rates observed in our sample of patients compared to the mortality rates observed by Shapiro et al[30] and by Hermans et al[37] during the validation of MEDS in a cohort of patients admitted to EDs. Basing on the excess of mortality found among our patients classified as "moderate risk" by MEDS with respect to those of validation cohorts (Table II), patients were divided into two groups (low-risk patients *vs.* high-risk patients) using as cut-off a MEDS score of 7 points. In other words, we compared very low/low-risk patients *vs.* moderate/high/very high-risk patients. To accomplish this, two-sample tests for equality of proportion were carried out. Consistently with previous results, a significantly higher proportion of mortality was found at 28-day among high-risk *vs.* low-risk patients (30.5% *vs.* 6.25%, p=0.045). A significantly higher proportion of mortality at 90-day was found among high-risk *vs.* low-risk patients (43% *vs.* 12.5%, p=0.022). Figure 4 shows Kaplan-Meyer curves for differences in survival

Table II. Mortality rates at 28-days and 90-days observed in our sample of patients and in those studied by Shapiro et al[30] and by Hermans et al[37].

MEDS	28-days mortality n (%)	90-days mortality n (%)	Shapiro et al[30] (%)	Hermans et al[37] (%)
Very low-risk	1 (4.3)	1 (3.0)	1.1	3.1
Low-risk	0 (0.0)	1 (3.0)	4.4	5.3
Moderate risk	11 (47.8)	19 (57.6)	9.3	17.3
High-risk	2 (8.7)	3 (9.1)	16.1	40
Very high-risk	9 (39.7)	9 (27.3)	39	77.8

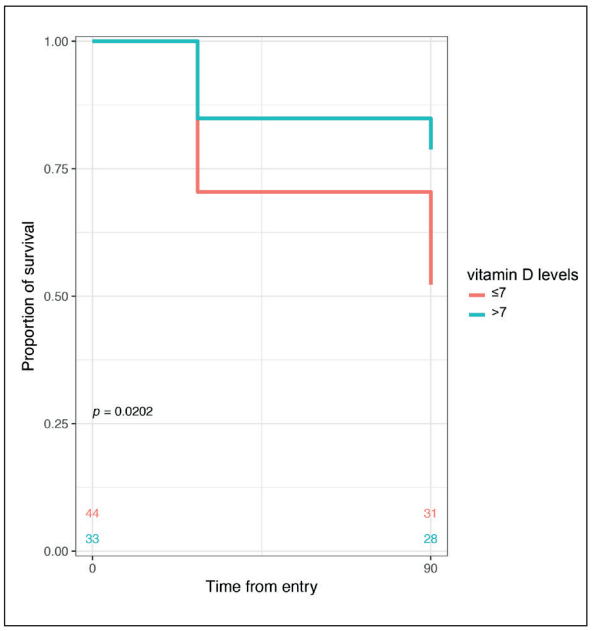

Figure 5. The Kaplan-Meyer curves for differences in survival proportion according to vitamin D levels.

proportion according to modified MEDS categories (p=0.026). Similarly, we explored the possibility to divide patients into two groups basing on their levels of vitamin D (low *vs.* high vitamin D levels), considering levels < 7 ng/ml (severe vitamin D deficiency) as cut-off. Consistently with previous results, a higher proportion of mortality was found at 28-day among patients with low *vs.* high vitamin D levels, without reaching statistical significance (29.5% *vs.* 15.2%, p=0.0698). A significantly higher proportion of mortality at 90-day was found among patients with low *vs.* high vitamin D levels (47.7% *vs.* 21.2%, p=0.0083). Figure 5 shows the Kaplan-Meyer curves for the differences in the survival proportion according to vitamin D levels (p=0.0202).

Discussion

The present investigation shows that MEDS score and low vitamin D levels are independent predictors of mortality, both at 28 days and at 90 days, in a cohort of microbiologically identified septic patients admitted to an Internal Medicine Inpatient Unit. There is a lack of data on clinical scores to predict the mortality of septic patients admitted to Internal Medicine wards[13]. According to some Authors, SCS and REMS could show the best performance in this setting when compared to MEDS and MEWS (modified early warning score)[16]. With this regard, a Italian study confirmed the lack of utility of MEWS in a similar population of septic patients[39]. However, if from one hand clinical characteristics of Internal Medicine patients (e.g., older age, clinical heterogeneity, multiple chronic diseases, and drug treatments) are thought to reduce the performances of most of the clinical scores[16], on the other hand, they increase the need for developing new ones or, at least, for validating old ones in this setting. In line with the literature data, our patients were elderly, with normal BMI[14]. A high prevalence of immunosuppression (41%), diabetes (40%) and neoplasms (39%) was found. Moreover, the majority of evaluated patients showed risk factors predisposing to infections[7,8]. The lactates levels were substantially normal, meaning that patients were not in the septic shock phase. The median procalcitonin levels were high, above the cut-off for sepsis (> 2 mmol/l). The mean SOFA score was high, while the mean qSOFA was low. These results confirm, at least in part, those by Giamarellos-Bourboulis et al[15] who found that SOFA showed a better sensitivity with respect to qSOFA for the early risk assessment of septic patients outside ICU. The prevalence of Gram-negative infections was slightly higher than Gram-positive, in line with the recent literature[40,41]. In addition, the 28-day and 90-day mortality was in line with the expected ones[7-9,28]. Contrarily to what expected[42], but in line with most of the literature, lactates, procalcitonin, and SOFA did not show any significant prediction of mortality[14]. On the contrary, qSOFA scores showed a significant association with mortality. This observation is in line with the literature data considering qSOFA as the score of choice for the identification of patients at risk of infection and poor prognosis in non-ICU wards[35,43]. Nevertheless, in our sample qSOFA was not an independent predictor of mortality.

In the current work, the only two independent predictors of mortality were MEDS score and low vitamin D levels. The utility of MEDS in predicting mortality is intelligible: it represents a score based on clinical parameters and risk factors for infection and disability, validated in the emergency setting[31]. However, this score did not perfectly fit with Internal Medicine patients. In fact, an excess of death among patients categorized as "moderate risk" has been observed in our sample with respect to the validation cohort. With this regard, a cut-off score of 7 (low *vs.* high-risk

patients) identified our patients at higher risk of mortality (Figure 4). This observation needs further confirmation and validation in a larger sample of Internal Medicine patients.

In line with the ICU literature and whit the only study available from Internal Medicine setting, the prevalence of vitamin D insufficiency was markedly high in our sample of patients (97.4%)[27]. Moreover, 57.1% of our septic patients showed severe vitamin D deficiency. According to the Italian Society for Osteoporosis, Mineral Metabolism and Bone Diseases (SIOMMMS) the prevalence of vitamin D deficiency reaches about 86% among Italian women over 70-year-old at the end of winter season[44]. Moreover, this prevalence grows exponentially among institutionalized subjects or among those with other concurrent diseases[44]. The high prevalence of severe vitamin D deficiency in our sample could confirm the susceptibility of this typology of patients (e.g., comorbid, elderly, institutionalized) to infections and sepsis. Moreover, a cut-off value of 7 ng/ml significantly predicted a higher risk of mortality (Figure 5). This observation needs future epidemiological studies in order to understand if the low vitamin D levels represent a causal factor for sepsis due to a reduced immune function, or an epiphenomenon due to increased tissue utilization associated to the inflammatory status[45]. Whether this observation could be related to the sepsis-associated immune paralysis remains to be understood[46]. Finally, as showed by ROC curves, the MEDS score represents a reliable test to predict mortality in our sample of septic patients. It is impressive that the simple value of vitamin D shows similar results in terms of AUC. However, as shown in Figure 4 and Figure 5, the AUC curves for 28-day and 90-day mortality are far from being optimal.

Conclusions

Sepsis represents a frequent disease for Internists and its approach is highly challenging. Although the increasing number of trials exploring this syndrome, there is ongoing uncertainty around the optimal management[47], probably because of the complexity of the syndrome and the high heterogeneity of septic populations[48]. Thus, "the certainty of evidence in what to do in sepsis has declined year over year"[47]. The present work shows for the first time that MEDS score and vitamin D represent two useful tests to predict prognosis of septic patients admitted to Internal Medicine wards. Currently, the role of vitamin D deficiency in predicting or influencing mortality of septic patients is not completely understood. We are far from having perfectly fitting tests, but they represent a reasonable start point for future studies in this setting.

Author's Contributions

AM, AT, VZ, MI, GP, CVV designed and coordinated the study; AC performed the statistical analysis; GV, GG, SDC, AG, GA, RL, participated in data acquisition. All Authors helped in data interpretation, drafted and approved the manuscript.

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Conflict of Interests

The Authors declare that they have no conflict of interests.

References

1) Reinhart K, Daniels R, Kissoon N, Machado FR, Schachter RD, Finfer S. Recognizing sepsis as a global health priority - a WHO resolution. N Engl J Med 2017; 377: 414-417.
2) Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, Angus DC, Reinhart K, International Forum of Acute Care Trialists. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. Am J Respir Crit Care Med 2016; 193: 259-272.
3) Liu V, Escobar GJ, Greene JD, Soule J, Whippy A, Angus DC, Iwashyna TJ. Hospital deaths in patients with sepsis from 2 independent cohorts. JAMA 2014; 312: 90-92.
4) Rudd KE, Delaney A, Finfer S. Counting sepsis, an imprecise but improving science. JAMA 2017; 318: 1228-1229.
5) Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001; 29: 1303-1310.
6) Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, Moreno R, Lipman J, Gomersall C, Sakr Y, Reinhart K, EPIC II Group of Investigators. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009; 302: 2323-2329.
7) Esteban A, Frutos-Vivar F, Ferguson ND, Peñuelas O, Lorente JA, Gordo F, Honrubia T, Algora A, Bustos A, García G, Diaz-Regañón IR, de Luna RR. Sepsis incidence and outcome: contrasting the intensive

care unit with the hospital ward. Crit Care Med 2007; 35: 1284-1289.

8) Vardi M, Ghanem-Zoubi NO, Bitterman H, Abo-Helo N, Yurin V, Weber G, Laor A. Sepsis in nonagenarians admitted to internal medicine departments: a comparative study of outcomes. QJM 2013; 106: 261-266.

9) Howell MD, Shapiro NI. Surviving sepsis outside the intensive care unit. Crit Care Med 2007; 35: 1422-1423.

10) Machado FR, Angus DC. Trying to improve sepsis care in low-resource settings. JAMA 2017; 318: 1225-1227.

11) Mazzone A, Dentali F, La Regina M, Foglia E, Gambacorta M, Garagiola E, Bonardi G, Clerici P, Concia E, Colombo F, Campanini M. Clinical features, short-term mortality, and prognostic risk factors of septic patients admitted to internal medicine units: results of an italian multicenter prospective study. Medicine (Baltimore) 2016; 95: e2124.

12) Mazzone A, Campanini M. Septic syndrome within internal medicine units: finally we have our records!. Italian J Med 2016; 10: 253-254.

13) Zaccone V, Tosoni A, Passaro G, Vallone CV, Impagnatiello M, Li Puma DD, De Cosmo S, Landolfi R, Mirijello A, Internal Medicine Sepsis Study Group. Sepsis in internal medicine wards: current knowledge, uncertainties and new approaches for management optimization. Ann Med 2017; 49: 582-592.

14) Ghanem-Zoubi N, Bitterman H, Laor A, Yurin V, Vardi M. The accuracy of clinical prediction of prognosis for patients admitted with sepsis to internal medicine departments. Ann Med 2015; 47: 555-560.

15) Giamarellos-Bourboulis EJ, Tsaganos T, Tsangaris I, Lada M, Routsi C, Sinapidis D, Koupetori M, Bristianou M, Adamis G, Mandragos K, Dalekos GN, Kritselis I, Giannikopoulos G, Koutelidakis I, Pavlaki M, Antoniadou E, Vlachogiannis G, Koulouras V, Prekates A, Dimopoulos G, Koutsoukou A, Pnevmatikos I, Ioakeimidou A, Kotanidou A, Orfanos SE, Armaganidis A, Gogos C, Hellenic Sepsis Study Group. Validation of the new Sepsis-3 definitions: proposal for improvement in early risk identification. Clin Microbiol Infect 2017; 23: 104-109.

16) Ghanem-Zoubi NO, Vardi M, Laor A, Weber G, Bitterman H. Assessment of disease-severity scoring systems for patients with sepsis in general internal medicine departments. Crit Care 2011; 15: R95.

17) 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.

18) Kempker JA, Tangpricha V, Ziegler TR, Martin GS. Vitamin D in sepsis: from basic science to clinical impact. Crit Care 2012; 16: 316.

19) Quraishi SA, De Pascale G, Needleman JS, Nakazawa H, Kaneki M, Bajwa EK, Camargo CA Jr, Bhan I. Effect of cholecalciferol supplementation on vitamin D status and cathelicidin levels in sepsis: a randomized, placebo-controlled trial. Crit Care Med 2015; 43: 1928-1937.

20) De Pascale G, Vallecoccia MS, Schiattarella A, Di Gravio V, Cutuli SL, Bello G, Montini L, Pennisi MA, Spanu T, Zuppi C, Quraishi SA, Antonelli M. Clinical and microbiological outcome in septic patients with extremely low 25-hydroxyvitamin D levels at initiation of critical care. Clin Microbiol Infect 2016; 22: 456.e7-456.e13.

21) Ala-Kokko TI, Mutt SJ, Nisula S, Koskenkari J, Liisanantti J, Ohtonen P, Poukkanen M, Laurila JJ, Pettilä V, Herzig KH, FINNAKI Study Group. Vitamin D deficiency at admission is not associated with 90-day mortality in patients with severe sepsis or septic shock: observational FINNAKI cohort study. Ann Med 2016; 48: 67-75.

22) Hewinson M. Antibacterial effects of vitamin D. Nat Rev Endocrinol 2011; 7: 337-345.

23) Amrein K, Schnedl C, Holl A, Riedl R, Christopher KB, Pachler C, Urbanic Purkart T, Waltensdorfer A, Münch A, Warnkross H, Stojakovic T, Bisping E, Toller W, Smolle KH, Berghold A, Pieber TR, Dobnig H. Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU randomized clinical trial. JAMA 2014; 312: 1520-1530.

24) https://clinicaltrials.gov/ct2/show/NCT03188796

25) https://clinicaltrials.gov/ct2/show/NCT03096314

26) Trongtrakul K, Feemuchang C. Prevalence and association of vitamin D deficiency and mortality in patients with severe sepsis. Int J Gen Med 2017; 10: 415-421.

27) Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G, SCCM/ESICM/ACCP/ATS/SIS. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003; 31: 1250-1256.

28) Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet 1974; 2: 81-84.

29) Keys A, Fidanza F, Karvonen MJ, Kimura N, Taylor HL. Indices of relative weight and obesity. Int J Epidemiol 2014; 43: 655-665.

30) Shapiro NI, Wolfe RE, Moore RB, Smith E, Burdick E, Bates DW. Mortality in emergency department sepsis (MEDS) score: a prospectively derived and validated clinical prediction rule. Crit Care Med 2003; 31: 670-675.

31) Kellett J, Deane B. The simple clinical score predicts mortality for 30 days after admission to an acute medical unit. QJM 2006; 99: 771-781.

32) Olsson T, Terent A, Lind L. Rapid emergency medicine score: a new prognostic tool for in-hospital mortality in nonsurgical emergency department patients. J Intern Med 2004; 255: 579-587.

33) Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, Reinhart CK, Suter PM, Thijs LG. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996; 22: 707-710.

34) Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, Rubenfeld G, Kahn JM, Shan-

kar-Hari M, Singer M, Deutschman CS, Escobar GJ, Angus DC. Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016; 315: 762-774.

35) Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM, Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2011; 96: 1911-1930.

36) R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Available online at https://www.R-project.org/.

37) Hermans MA, Leffers P, Jansen LM, Keulemans YC, Stassen PM. The value of the mortality in emergency department sepsis (MEDS) score, C reactive protein and lactate in predicting 28-day mortality of sepsis in a Dutch emergency department. Emerg Med J 2012; 29: 295-300.

38) Tirotta D, Gambacorta M, La Regina M, Attardo T, Lo Gullo A, Panzone F, Mazzone A, Campanini M, Dentali F. Evaluation of the threshold value for the modified early warning score (MEWS) in medical septic patients: a secondary analysis of an Italian multicentric prospective cohort (SNOOPII study). QJM 2017; 110: 369-373.

39) Pop-Vicas A, Tacconelli E, Gravenstein S, Lu B, D'Agata EM. Influx of multidrug-resistant, gram-negative bacteria in the hospital setting and the role of elderly patients with bacterial bloodstream infection. Infect Control Hosp Epidemiol 2009; 30: 325-331.

40) Klotz SA, Chasin BS, Powell B, Gaur NK, Lipke PN. Polymicrobial bloodstream infections involving Candida species: analysis of patients and review of the literature. Diagn Microbiol Infect Dis 2007; 59: 401-406.

41) 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 2016; 315: 801-810.

42) Gai L, Tong Y, Yan BQ. Research on the diagnostic effect of PCT level in serum on patients with sepsis due to different pathogenic causes. Eur Rev Med Pharmacol Sci 2018; 22: 4238-4242.

43) Rannikko J, Seiskari T, Huttunen R, Tarkiainen I, Jylhävä J, Hurme M, Syrjänen J, Aittoniemi J. Plasma cell-free DNA and qSOFA score predict 7-day mortality in 481 emergency department bacteraemia patients. J Intern Med 2018; 284: 418-426.

44) Adami S, Romagnoli E, Carnevale V, Scillitani A, Giusti A, Rossini M, Gatti D, Nuti R, Minisola S, Italian Society for Osteoporosis, Mineral Metabolism and Bone Diseases (SIOMMMS). Guidelines on prevention and treatment of vitamin D deficiency. Reumatismo 2011; 63: 129-147.

45) Koekkoek WA, van Zanten AR. Vitamin D deficiency in the critically ill. Ann Med 2016; 48: 301-304.

46) Feuerecker M, Sudhoff L, Crucian B, Pagel JI, Sams C, Strewe C, Guo A, Schelling G, Briegel J, Kaufmann I, Choukèr A. Early immune anergy towards recall antigens and mitogens in patients at onset of septic shock. Sci Rep 2018; 8: 1754.

47) Abbasi J. In treating sepsis, questions about timing and mandates. JAMA 2017; 318: 506-508.

48) Berger D, Schefold JC. Life ain't no SOFA-considerations after yet another failed clinical sepsis trial. J Thorac Dis 2017; 9: 438-440.