Use of the SINBAD score as a predicting tool for major adverse foot events in patients with diabetic foot ulcer: A French multicentre study

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Georges Ha Van1 | Sophie Schuldiner2 | Ariane Sultan3,4 | Benjamin Bouillet5,6,7 | Jacques Martini8 | Julien Vouillarmet9 | Medhi Menai10 | Aurélie Foucher10 | Olivier Bourron11 | Agnes Hartemann11 | Antoine Perrier1

1 Diabetes Department, APHP, Hospital Pitie Salpetriere, Paris, France

2 Endocrinology Department, University Hospital Center, Nimes, France

3 Nutrition-Diabetes Department, University Hospital of Montpellier, Montpellier, France

4 PhyMedExp, INSERM U1046, CNRS UMR 9214, University of Montpellier, Montpellier, France

5 Endocrinology and Diabetology Department, University Hospital Center, Dijon, France

6 INSERM, Dijon, France

7 University of Bourgogne Franche-Comté, LNC UMR1231, Dijon, France

8 Endocrinology Department, University Hospital Center, Toulouse, France

9 Endocrinology Department, University Hospital Center, Lyon, France

10 IHU ICAN, Foundation for Innovation in Cardio Metabolism and Nutrition, Paris, France

11 Diabetes Department, Sorbonne University, AP-HP, Hôpital Pitié-Salpêtrière, Paris, France

Correspondence

Georges Ha Van, Diabetes Department, APHP, Hospital Pitie Salpetriere, Paris

KEYWORDS

diabetic foot ulcer, major adverse foot event, SINBAD

Abstract

Objective:

To assess the relationship between the site, ischaemia, neuropathy, bacterial infection, area, depth (SINBAD) score and major adverse foot events in patients with diabetes and foot ulcers.

Methods:

For this retrospective ancillary study, patients (n = 537) followed for a diabetic foot ulcer (DFU) in six French hospitals were included between 1 February 2019 and 17 March 2019, and between 1 February 2020 and 17 March 2020. The SINBAD score was assessed at inclusion. The frequency of a composite outcome consisting of eight major adverse foot events (MAFE) was assessed after 5–6 months of follow-up: hospitalisation for DFU, septic surgery, revascularisation, minor amputation, major amputation, death, secondary infection and ulcer recurrence. A logistical regression explored the link between the SINBAD score and MAFE and each of its component.

Results:

A low SINBAD score (from 0 to 3) was observed in 61% of patients and a high (from 4 to 6) in 39%. MAFE occurred in, respectively, 24% and 28% of these patients. Multivariate analyses showed a significant relationship between the SINBAD score and MAFE, with the continuous SINBAD score: odds ratio (OR) 1.72 [95% CI (1.51–1.97)] or dichotomic SINBAD score (values: 0–3 and 4–6): OR 3.71 [95% CI (2.54–5.42)]. The SINBAD score (continuous or dichotomic) at inclusion was also significantly associated with six out of the eight components of the MAFE.

Conclusions:

The SINBAD score is a useful tool for predicting major adverse foot events.

1 | INTRODUCTION

Diabetic foot ulcer (DFU) is a huge public health problem, with an estimated cost of approximately $80 billion in 2017 in the United States.[1] A multidisciplinary approach is recommended to resolve the variety of problems that arise in DFU management, often requiring offloading, infection treatment, septic surgery (SS), revascularisation, topical care, optimization of glycaemic control, and undernutrition prevention.[2] Several studies have shown the effectiveness of this unified approach to diabetic foot care, which reduces amputation risk by 45%–55%.[3–6] The International Working Group of the Diabetic Foot (IWGDF) 2019 guidelines on DFUs concluded that key useful factors for scoring DFUs are of three types: patient-related (end-stage renal failure), limb-related (peripheral arterial disease (PAD) and loss of protective sensation), and ulcer-related (area, depth, site, single or multiple, and infection).[7] The site, ischaemia, neuropathy, bacterial infection, area, depth (SINBAD) scoring system (site, ischaemia, neuropathy, bacterial infection, area, depth), which includes six out of these eight factors, is an easy-to-use scoring system that can reach a maximum of six points (Supplemental Table 1) and is recommended by the IWGDF for the follow-up of patients with a DFU.[7]

The relationship between healing time and ulcer area, ulcer site, and PAD has been demonstrated.[8] The SINBAD score shows a clear step-up in time to healing between scores of 2 and 3, suggesting that DFUs with a score of 3 or greater are at particular risk of poor foot outcomes.[9] The cut-off of the SINBAD severity score in relation to the prognosis for healing or amputation is around 3, and this scoring has been validated with good reliability and reproducibility for both ulcer healing and amputation prediction.[7,10–23] However, the association between the SINBAD score and adverse events (AEs), such as the occurrence of infection, revascularisation, SS, hospitalisation, death, or ulcer recurrence, has never been studied.

The main objective of this study was to assess the relationship between the SINBAD score and the risk of occurrence of at least one major adverse foot event (MAFE), defined as a composite of eight AEs: hospitalisation, SS, revascularisation, minor amputation (MinA), major amputation (MajA), death, infection and ulcer recurrence. Our hypothesis was that a high score on the SINBAD, a system that is easy to use for non-specialists, would be a predictive factor for MAFE. The secondary objective was to assess the relationship between the SINBAD score and the occurrence of each of the eight AEs.

2 | METHODS

2.1 | Study design and data collection

This was an ancillary study of a retrospective study (COVIPIED) comparing DFU outcomes in terms of MAFE between two periods: period 1 from 1 February 2019 to 17 March 2019 with a follow-up period up to 1 August 2019 (cohort 1), and period 2: 1 from February 2020 to 17 March 2020 with a follow-up period up to 1 August 2020 (cohort 2). This second period included the COVID-19 lockdown, which lasted from 16 March to 11 May 2020, in France.

The data sources were the discharge databases and the medical records, and all collected data was anonymous. The patient data from the two cohorts were pooled for analysis.

The study received approval from the Ethics and Research Committee of Sorbonne University on 18 January 2021 (Protocol number CER-2020-99). Six French multidisciplinary diabetic foot care departments (DFCDs) participated in this multicenter study (Montpellier, Dijon, Nimes, Lyon, Toulouse, and Paris). The inclusion criteria were as follows: patients over 18 years old with a DFU evolving for fewer than 12 months.

The exclusion criteria were as follows: leg or malleolar ulcer; a wound secondary to MinA of less than 4 weeks; missing data on age, gender, body mass index (BMI) and SINBAD score; and lost to followup on 1 August 2019 (cohort 1) or 1 August 2020 (cohort 2).

All successive outpatients attending a DFCD with these criteria were included. In the case of two DFUs, the oldest one was included. The DFUs were clinically checked during monthly consultations. All patients received DFU management in accordance with the guidance recommendations.24

The collected data included age, sex, history of DFU, duration of diabetes, BMI, HbA1c, insulin therapy, and end-stage renal disease. The SINBAD score was assessed at inclusion (arrival at the DFCD).

The SINBAD score9 was calculated with six factors graded from 0 to 1: site, ischaemia, neuropathy, bacterial infection, area, and depth (Supplemental Table 1). The ulcer site was scored as 0: for forefoot (distal to tarso-metatarsal joint) or 1: for midfoot or hind foot. Ischaemia was scored as 0: at least one pulse palpable (blood flow relatively intact on the affected foot) or 1: no pulse palpable with signs of poor perfusion (cold feet, skin discolouration, slower hair growth, swelling, cramping) with or without gangrene. Neuropathy, or loss of protective sensation on the basis of examination using 10-g nylon monofilaments, was scored as 0: absent or 1: present. Bacterial infection, defined as clinical signs of infection of either soft tissues or bone (as proposed by the infectious disease society of america (IDSA) and IWGDF), was scored as 0: absent or 1: present). Area, or the two maximum dimensions at right angles multiplied, was scored as 0: <1 cm2 or 1: >1 cm2. Last, depth was scored as 0: superficial or 1: deep-reaching muscle, tendon, joint capsule or bone. The SINBAD score was obtained by summing the components of the classification, creating a SINBAD score range of 0–69 (Supplemental Table 1).

Every AE was related to the original DFU.

2.2 | Definitions of outcomes

A MAFE was defined as a composite outcome consisting of the occurrence of at least one of these eight AEs in relation to the initial DFU: hospitalisation (H), SS, revascularisation (Rev), MinA, MajA, death (D), secondary infection (SI), and DFU recurrence (Rec).

Secondary infection of the initial DFU was defined as purulent discharge with two other local signs (warmth, erythema, lymphangitis, lymphadenopathy, oedema, or pain) or cellulitis during follow-up and was classified according to the IDSA-IWGDF classification: grade 2, 3 or 4.24

Hospitalisation (H) was defined as hospitalisation during followup in the case of a DFU that had become complicated with wet gangrene, abscess, fever, signs of sepsis, critical limb ischaemia and the need for revascularisation, SS (soft tissue and/or bone), or parenteral antibiotic therapy.

Septic surgery was defined as soft tissue infection surgical debridement of the initial DFU with or without bone resection during follow-up. This could range from minor bedside debridement or incision and drainage to major operative procedures including resection of deep infected tissue, drainage of abscesses or infected compartments, and resection of necrotic or infected bone in accordance with IWGDF 2019 recommendations.25

Revascularisation (Rev) was defined as percutaneous transluminal angioplasty or bypass during the follow-up provided to improve healing of the initial DFU. In accordance with IWGDF recommendations, we considered vascular imaging to assess the need for revascularisation in a patient with DFU and PAD, irrespective of the results of bedside tests, when the DFU had not healed within 4–6 weeks despite optimal management.26

Recurrence (Rec) of DFU was defined as recurrence at the same DFU localization.

Amputation was defined as the complete loss in the transverse anatomical plane of any part of the lower limb. Minor amputation was defined as removal of a part of the foot distal to the transverse tarsal joint with preservation of the talus and calcaneus (Chopart, Lisfranc, total or partial transmetatarsal or toe amputations), whereas MajA was defined as above ankle amputation (transtibial or transfemoral).

2.3 | **Statistical analyses**

Continuous and categorical variables are summarised as means +/- standard deviation (SD) and percentages, respectively.

Potentially co-founding factors (as listed in the baseline characteristics section) between MAFE and its component and SINBAD and its component were initially identified through bivariate analyses and selected for multivariate logistic analyses [expressed as odds ratios with 95% CI] if $p < 0.2$.

Multivariate logistic models were constructed independently for each MAFE component and for the occurrence of at least one of its components, meaning each model had a different set of covariables. Age, sex, and BMI were included in each model. All statistical analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC, USA).

TABLE 1 Characteristics of the population, SINBAD score and components at inclusion.

	N	%
Age (years)	537	69.0 ± 12.4
Men,%	537	75.8
Body Mass index (kg/cm^2)	537	28.5 ± 5.5
Diabetes duration (years)	481	21.2 ± 12.9
History of ulcers, %	520	69.6
Insulin, %	523	72.1
Haemodialysis %	510	13.7
HbA1c %	424	8.0 ± 1.8
SINBAD score	537	3 ± 1.5
SINBAD = 0	537	1.1
SINBAD = 1	537	19.4
SINBAD = 2	537	21.6
SINBAD = 3	537	19.2
SINBAD = 4	537	18.8
SINBAD = 5	537	16.2
SINBAD = 6	537	3.7
Site S1	537	21
Ischaemia I1	537	39.5
Neuropathy N1	537	96.8
Bacteria B1	537	44.3
Area A1	537	47.9
Depth D1	537	49.2

Abbreviation: SINBAD, site, ischaemia, neuropathy, bacterial infection, area, depth.

3 | RESULTS

Of the 713 patient records, 537 were included as they were in accordance with the inclusion and exclusion criteria. Although two different cohorts were used, there were no significant differences between them at inclusion or for AEs.

3.1 | Baseline characteristics

Baseline characteristics of patients and SINBAD scores at inclusion are shown in Table 1. The average age was 69.0 +/- 12.4 years with 75.8% men.

SINBAD groups 0–3 and 4–6 did not differ for age (68.8 years old vs. 69.3, $p = 0.64$), diabetes duration (21.0 years vs. 21.6, $p = 0.60$), history of ulcers (72% vs. 65.8%, $p = 0.14$), insulin treatment (69.2% vs. 76.7%, $p = 0.06$) and HbA1c (8% vs. 7.9%, $p = 0.45$), but the SINBAD group 0–3 comprised less men (72.3% vs. 81.3%, $p = 0.02$), had higher BMI (29.1 vs. 27.6, $p = 0.001$) and had less haemodialysis (10.6% vs. 18.6%, $p = 0.01$).

No interaction was found between MAFE and the SINBAD score with patient characteristics.

The average SINBAD score was 3 +/- 1.5. A low SINBAD score (from 0 to 3) was found for 61% ($n = 329$) of the patients and a high SINBAD score (from 4 to 6) for 39% ($n = 208$) (Table 1). Major adverse foot events occurred, respectively, in 24% ($n = 130$) and 28% occurred, respectively, in 24% ($n = 130$) and 28% ($n = 149$) of these patients (Table 2). Table 2 also shows every AE per SINBAD score and the SINBAD 0–3 and 4–6 subgroups.

3.2 | Association between SINBAD score and major adverse foot event risk

The mean rate of MAFE was 52% ($n = 279$). The mean rate of separate AEs within the follow-up period (with a range of patient data between 473 and 530) were as follows: hospitalisation: 27% ($n = 143$), SS: 8.8% ($n = 46$), revascularisation:15.2% ($n = 78$), MinA:15.6% ($n = 82$), MajA: 7% ($n = 37$), SI: 38.4% ($n = 188$), death: 4.5% ($n = 23$), and recurrence: 4.2% ($n = 20$).

Multivariate analysis showed a positive association between a continuous SINBAD score and MAFE. If the SINBAD score increased by one unit (e.g., when the patient moved from 2 to 3 or from 5 to 6), this one-unit increase was significantly associated with an increased risk of MAFE (1.72 CI [1.51–1.97] (Table 3). In addition, there was a significant association between a continuous SINBAD score and an increased risk of six out of eight separate AEs (except for death and DFU recurrence): hospitalisation (1.29; CI [1.12–1.47]), SS (1.46; CI [1.15–1.86]), revascularisation (1.85; CI [1.49–2.29]), MinA (1.54; CI [1.30–1.84]), MajA (2.38; CI [1.73–3.28]), and SI (1.85 CI [1.59–2.15]) (Table 3).

Furthermore, multivariate analysis also showed a positive association between a dichotomic SINBAD score and MAFE. The comparison of the two groups of SINBAD scores (0–3 and 4–6) showed that the 4–6 SINBAD group was significantly associated with an increased risk of MAFE (3.71 CI [2.54–5.42]) (Table 3) along with a positive association between the dichotomic SINBAD score and the risk of six out of eight separate AEs (except for death and DFU recurrence): hospitalisation (1.87 [1.24–2.80]), SS (2.89 [1.42–5.90]), revascularisation (5.21 [2.83–9.60]), MinA (2.89 [1.75–4.78]), MajA (7.98 [3.19–19.93]), and SI (5.56 [3.65–8.46]) (Table 3).

TABLE 2 Adverse events (AEs) per Sinbad score.

Sinbad Score(*n*)	MAFE *n* (%)	Hospitalisation *n* (%)	Septic Surgery *n* (%)	Rev *n* (%)	Min A. *n* (%)	MajA. *n* (%)	Death *n* (%)	Secondary Infection *n* (%)	Rec *n* (%)
0 (6)	2 (33.3)	1 (16.7)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)	2 (33.3)	0 (0)
1 (104)	25 (24)	13 (12.5)	5 (4.8)	1 (1)	3 (2.9)	1 (1)	0 (0)	15 (14.4)	6 (5.7)
2 (116)	39 (33.6)	22 (18.9)	3 (2.5)	9 (7.7)	8 (6.9)	0 (0)	4 (3.4)	19 (16.3)	5 (4.3)
3 (103)	64 (62.1)	36 (34.9)	9 (8.7)	14 (13.5)	20 (19.4)	6 (5.9)	8 (7.7)	34 (37.4)	3 (2.9)
4 (101)	69 (68.3)	40 (39.6)	11 (10.8)	23 (22.7)	25 (24.7)	7 (6.9)	2 (1.9)	50 (49.5)	5 (4.9)
5 (87)	66 (75.9)	25 (28.7)	15 (17.2)	27 (31)	24 (27.5)	17 (19.5)	5 (5.7)	56 (64.3)	1 (1.1)
6 (20)	14 (70)	6 (33.3)	3 (15)	5 (25)	2 (10)	6 (30)	3 (15.0)	12 (60)	0 (0)
0–3	130 (39.5)	72 (22.2)	17 (5.3)	24 (7.6)	31 (9.6)	7 (2.2)	13 (4.2)	70 (23)	14 (4.8)
4–6	149 (71.6)	71 (34.6)	29 (14.6)	55 (28.1)	51 (25.5)	30 (14.9)	10 (5.2)	118 (63.8)	6 (3.3)

Abbreviations: DFU, Diabetic foot ulcer; MAFE, Major adverse foot event; MajA, major amputation; MinA, minor amputation; Rec, Recurrence of DFU; Rev, revascularisation.

TABLE 3 Multivariate logistic association between SINBAD score and adverse events (AEs) of patients with diabetic foot ulcers (DFUs).

Adverse event (*n* = available data)	SINBAD score (0–6, continuous)	SINBAD score (0–3/4–6, dichotomic)
MAFE (*n* = 537)	1.72 (1.51–1.97)	3.71 (2.54–5.42)
Hospitalisation (*n* = 513)	1.29 (1.12–1.47)	1.87 (1.24–2.80)
Septic surgery (*n* = 414)	1.46 (1.15–1.86)	2.89 (1.42–5.90)
Revascularisation (*n* = 382)	1.85 (1.49–2.29)	5.21 (2.83–9.60)
Minor amputation (*n* = 507)	1.54 (1.30–1.84)	2.89 (1.75–4.78)
Major amputation (*n* = 499)	2.38 (1.73–3.28)	7.98 (3.19–19.93)
Death (*n* = 506)	1.30 (0.98–1.73)	1.16 (0.49–2.75)
Secondary infection (*n* = 465)	1.85 (1.59–2.15)	5.56 (3.65–8.46)
Recurrence (*n* = 446)	0.75 (0.49–1.15)	0.60 (0.16–2.27)

Note: Values are Odd ratios and 95% confidence interval limits. Models were adjusted on age, sex and body mass index. Models were subsequently adjusted on history of DFU, HBA1c, a need for dialysis, diabetes duration, and insulin if bivariate analyses showed $p < 0.2$.

Abbreviations: MAFE, Major adverse foot event; SINBAD, site, ischaemia, neuropathy, bacterial infection, area, depth.

3.3 | Multivariate logistic association between SINBAD components and AEs of patients with DFU23

There were significant associations between four SINBAD score components and AE (Supplemental table 2).

- Site (score 1: midfoot/hindfoot) and major amputations (2.63 [1.19–5.82]).

- Ischaemia (score 1: signs of ischaemia) and MAFE (1.97 [1.31–2.98]), hospitalisation (2.03 [1.31–3.14]), revascularisation (9.19 [4.35–19.4]), MinA (2.01 [1.15–3.50]), MajA (3.67 [1.42–9.47]), and death (3.05 [1.12–8.36]).

- Bacterial infection (score 1: present) and MAFE (4.47 [2.70–7.41]), hospitalisation (1.91 [1.09–3.34]), SS (2.97 [1.07–8.26]), revascularisation (2.32 [1.00–5.37]), MinA (5.34 [2.38–11.98]), and SI (6.66 [3.75–11.81]).

- Area (score 1: >1 cm2) and revascularisation (2.21 [1.14–4.30]), MajA (3.17 [1.21–8.34]), and death (3.11 [1.08–8.98]).

4 | DISCUSSION

To our knowledge, this is the first multicenter study that has explored the association between the SINBAD score and secondary MAFE in patients with DFU. We highlighted a strong significant association between the SINBAD score (continuous or dichotomic: 0–3 and 4–6) at inclusion and MAFE risk. We defined this composite outcome including eight classic MAFE: hospitalisation, SS, SI, revascularisation, MinA, MajA, ulcer recurrence, and death.

Until now, the validity of the SINBAD score has relied on its association with the chance of ulcer healing and the risk of MajA.15 A SINBAD score <3 is associated with a healing rate of 60% at 12 weeks compared with 35% if the score is > 3, and a risk of MajA at 6 months of 2.7% versus 0.7%.23 A 2021 study27 found a 100% healing rate in patients with a SINBAD score of 0 versus 49% in patients with a SINBAD score of 6, with a stepwise decrease in the proportion of ulcers healing with each increase in the score. DFUs classified into SINBAD category 4 were 28%, SINBAD 0: 0.7% and SINBAD 1: 4.5%.27 Furthermore, Alasabeck et al. showed a median healing time of 14 weeks in patients with a SINBAD score ≥3 and 4 weeks in patients with a SINBAD score ≤ 2.28

Two recent studies found that a high SINBAD score was associated with the presence of DFU infection with extended-spectrum beta-lactamase (ESBL)-producing bacteria29 or Meti-R Staph aureus.30 In 2019, the IWGDF issued a strong recommendation to use the SINBAD system for communications among health professionals on the characteristics of a foot ulcer in a person with diabetes. For this purpose, it is important to use the individual clinical descriptors and not merely the total score. This classification has been validated for both ulcer healing and amputation prediction.7

Our results showed that the SINBAD score is also useful to predict relevant MAFE. We explored this association using a composite outcome MAFE. One unit of the score increased the risk of MAFE by 1.7. Patients with a SINBAD score of 4–6 had an increased risk of MAFE of 3.7 compared with patients with a SINBAD score 0–3. These data reinforce the usefulness of this score.

The population was representative of the usual patients seen in specialised DFU centres, who generally have a rather high average SINBAD score. Mortality rate and minor and MajA rates were similar to what is described in the literature.29–32

The SINBAD score during follow-up was associated with a significant increased risk of hospitalisation, SI, revascularisation, SS, and, as already known, minor and major amputations. The short duration of follow-up probably explains the absence of an association with death and ulcer recurrence. Mortality is often associated with the presence of a DFU, but only after a long follow-up.33,34 A recent study with a median follow-up of 8 years demonstrated that the SINBAD score is a predictor of mortality.35 Although DFU is not the direct cause of death (which is instead due to associated comorbidities such as PAD, endstage renal disease, coronary heart disease, stroke), some authors consider that it is an independent risk factor for mortality.1

Our study also confirmed in more than 500 patients that the components of the SINBAD score were relevant.23 Ischaemia and infection at DFU presentation were associated with MAFE and five of the components of MAFE. This showed the predominance of these two components of the SINBAD score in the prognosis of the severity in DFU management. We should note that one of the weaknesses of the SINBAD score is that it attributes the same scores for ischaemia and infection and neuropathy and area or depth. Site, ischaemia, and area predicted the risk of MajA. Surprisingly, we found no independent association of depth with MAFE or any of the MAFE components, whereas in one study, depth was the only common item among multiple centres to be associated with outcome.9

As specified by the IWGDF 2019 guidelines, the interest of the SINBAD score lies in its ability to provide indications of the prognosis of the DFU. The six items of the SINBAD score describe rather well the usual characteristics of the severity of DFUs. In 2008, the authors of one study concluded that the SINBAD score may offer a system for defining the DFU type that could be applied worldwide.9. The objective of the present study was to use SINBAD system, noted for its simplicity, to evaluate its relevance to predict outcomes, even in poorly equipped centres. For non-specialists, diabetes alone is often considered responsible for secondary AEs.

The International Diabetic Foot Care Group, in collaboration with DFoot International, developed the Fastrack Pathway (FTP), which proposes practical integrated treatment, spanning primary care and dedicated diabetic foot services. In the UK, the SINBAD score is used in the English version of the FTP.36 The composite outcome MAFE might complete the usefulness of the SINBAD score, just as composite major adverse cardiovascular event (MACE) does in the chest pain of cardiovascular patients.37

The limitations of our study included a short follow-up period, a retrospective design, and the absence of information on ulcer healing. Also, of the 713 cases, only 75% were included in the study and this may have resulted in selection bias. Further, recruitment was limited to specialised DFU centres, meaning that generalizations should be made with caution (particularly with regard to the checking of ischaemia, which can easily be much more precise than simple pulse taking and the clinical aspect in these six DFU specialised centres). The strengths of our study were the multicenter aspects, the large number of patients, and the variety of AEs studied. We showed that the SINBAD score could be used beyond the simple prognosis of healing and amputation to assess the risk of MAFE in a study where not only were the demographics consistent with the literature but also the SINBAD scores were rather high.

5 | CONCLUSION

The SINBAD scoring system is simple and quick to use, not requiring special equipment beyond clinical examination alone and containing the necessary information to allow for triage by a specialist team.

We showed that the SINBAD score can be used by clinicians beyond the simple prognosis of healing and amputation to assess the risk of MAFE, since each unit of SINBAD and a score > 4 were associated with an increased risk of MAFE and most of its components.

Furthermore, for DFU management, we propose to use a composite outcome MAFE, which is similar to MACE in patients with cardiovascular risk.

AUTHOR CONTRIBUTIONS

Georges Ha Van had full access to all the data in the study and wrote the article. Antoine Perrier, Medhi Menai independently extracted the related data information. Georges Ha Van, Antoine Perrier, Aurélie Foucher, Medhi Menai conceived the study concept and design. Georges Ha Van, Benjamin Bouillet, Ariane Sultan, Sophie Schuldiner, Jacques Martini, Julien Vouillarmet included patients of the study. Georges Ha Van, Sophie Schuldiner, Ariane Sultan, Jacques Martini, Julien Vouillarmet, Benjamin Bouillet, Olivier Bourron, Aurélie Foucher, Agnes Hartemann, Antoine Perrier, Medhi Menai contributed to the critical revision of the manuscript. All authors have read and approved the final manuscript.

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Georges Ha Van is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

CONFLICT OF INTEREST STATEMENT

The authors have declared no potential conflict of interest relevant to this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors declare that they adhere to the recommendations of the Wiley Publishing ethics guidelines: Declare to your chosen journal that your manuscript is not published elsewhere. Check all co-authors meet criteria for authorship and ensure appropriate acknowledgements made in the manuscript. Include appropriate funding statements in the manuscript. Show informed consent and provide assurances that participants' rights are protected*. Register clinical trial: The study received approval from the Ethics and Research Committee of Sorbonne University on 18 January 2021 (Protocol number CER-2020-99). Be alert to bias

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