



ORIGINAL

A prospective, observational severe sepsis/septic shock registry in a tertiary hospital in the province of Guipuzcoa (Spain)[☆]

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KEYWORDS

Severe sepsis;
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Abstract

Objective: To determine the epidemiological and clinical characteristics of the patients with severe sepsis/septic shock admitted to the Intensive Care Unit (ICU) of Donostia Hospital (Guipuzcoa, Spain), analyzing the prognostic factors and comparing them with the existing data at national level.

Design: A prospective observational study was carried out during a consecutive 3-year period (1 Feb. 2008–31 Dec. 2010).

Setting: The ICU of Donostia Hospital, the only third level hospital in the province of Guipúzcoa, with a recruitment population of 700,000 inhabitants.

Results: In the course of the study period, 6263 patients were admitted to our department: 2880 were non-coronary patients, and 511 suffered a severe sepsis or septic shock episode upon admission or during their stay in the ICU. Males predominated (66.5%), the mean age was 63 years, and the mean Acute Physiology And Chronic Health Evaluation II (APACHE II) score was 21. Most cases were medical (68%) and were admitted from hospital wards (53.5%). The most frequent origin was pneumonia (24%). The great majority of the cases (73%) corresponded to septic shock. Hemodynamic alterations were the most frequent disorders, followed by renal and respiratory impairment. Noradrenalin was used as vasoactive drug in all shock patients; over one-half required mechanical ventilation (MV), and one-third required continuous venous–venous hemodiafiltration (CVVHDF). Interventions frequently used in the management of these patients comprised blood cultures or corticosteroid use, while other measures such as activated protein C were little used. The mortality rate in the ICU was 20.8%, with a mean stay in the Unit of 14 days. The parameters associated to mortality in the multivariate analysis included the presence of hypoglycemia, respiratory dysfunction, the need for MV, lactic acid elevation and thrombocytopenia in the first 24 h, together with an origin of sepsis either in the ICU or in the hospital.

Conclusions: Severe sepsis is frequent in our unit, generating important morbidity and hospital stay, as well as high mortality. The epidemiological and clinical characteristics of our patients are similar to those described globally at national level. Considering our data in complying with the different treatment measures, it is clear that there is still room for improvement.

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PALABRAS CLAVE

Sepsis grave;
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Mortalidad

Registro observacional y prospectivo de sepsis grave/shock séptico en un hospital terciario de la provincia de Guipúzcoa

Resumen

Objetivo: Conocer las características epidemiológicas y clínicas de los pacientes con sepsis grave/shock séptico ingresados en la unidad de cuidados intensivos del Hospital Donostia, analizar factores pronósticos y compararlos con los datos existentes a nivel nacional.

Diseño: Estudio observacional prospectivo durante un periodo consecutivo de 3 años (1 de febrero de 2008–31 de diciembre de 2010).

Ámbito: Unidad de cuidados intensivos (UCI) del Hospital Donostia, único hospital de tercer nivel de la provincia de Guipúzcoa, que atiende a una población de 700.000 habitantes.

Resultados: A lo largo de este periodo, 6.263 pacientes ingresaron en nuestro servicio; 2.880 fueron pacientes no coronarios y 511 presentaron al ingreso o en su evolución en UCI, un episodio de sepsis grave o shock séptico. Hubo un predominio de varones (66,5%), con una edad media de 63 años y *Acute Physiology And Chronic Health Evaluation II* (APACHE II) medio de 21. La mayoría fueron de tipo médico (68%), procedentes de planta de hospitalización (53,5%) y el origen más frecuente fue la neumonía (24%). La gran mayoría (73%) presentó shock séptico. La afectación hemodinámica fue la más frecuente, seguida de la renal y respiratoria. En todos los pacientes con shock se utilizó noradrenalina como vasopresor, más de la mitad requirieron ventilación mecánica (VM) y un tercio, hemodiafiltración venovenosa continua (HDFVVC). En el manejo de estos pacientes hubo medidas con aplicación elevada como la realización de hemocultivos o el uso de corticoides pero otros de escasa aplicación como la proteína C activada. La mortalidad en UCI fue del 20,8%, con una estancia media intra-UCI de 14 días. Las variables asociadas a la mortalidad en el análisis multivariante incluyen la presencia de hipoglucemia, la disfunción respiratoria, necesidad de ventilación mecánica, hiperlactacidemia y presencia de trombocitopenia en las primeras 24 horas junto con el origen de la sepsis en UCI o intrahospitalaria.

Conclusión: La sepsis grave es una afección frecuente en nuestra unidad, genera elevada morbilidad y tiempo de estancia hospitalaria, además de una alta mortalidad. Las características epidemiológicas y clínicas de nuestros pacientes son similares a las referidas a nivel nacional. Teniendo en cuenta nuestros datos en el cumplimiento de las diferentes medidas de tratamiento, es evidente que quedan aspectos que mejorar.

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Introduction

Sepsis is characterized by important morbidity–mortality, especially when associated to organ dysfunction and/or shock. In Spain, the reported incidence of severe sepsis is 104 per 100,000 inhabitants/year, with a mortality rate of 20.5%, while the incidence of septic shock is 31 per 100,000 inhabitants/year, with a mortality rate of 45.7%.¹ The Surviving Sepsis Campaign (SSC) was launched in the year 2002 with the purpose of reducing mortality due to sepsis through the development and implementation of clinical practice guides.² In Spain, the Edu-sepsis project,^{3,4} in which we participated, reaffirmed the importance of educational campaigns for the implementation of guides, and afforded further data on the prevalence and mortality of this disease at national level. After participating in that study, we decided to create a database of our own, with the following objectives:

- To determine the impact of severe sepsis in our ICU, which belongs to the only third-level hospital center in Guipúzcoa and attends over 90% of all critical patients in our province.
- To analyze prognostic factors.

- To compare our results with those reported in other studies, particularly at national level.
- To determine our degree of compliance with the clinical guides and identify those aspects which must be improved.

Material and methods

A prospective observational study was carried out over a period of 35 consecutive months (from 1 February 2008 to 31 December 2010), involving those patients with septic shock/severe sepsis upon admission to the ICU or who developed septic shock/severe sepsis during their stay in the ICU, in accordance with the definitions of the International Sepsis Definitions Conference of 2001.⁵

Our ICU has 48 beds and belongs to the only third-level hospital center in the province of Guipúzcoa, with a recruitment population of 700,000 inhabitants. It is the only critical care unit in the province equipped with extracorporeal filtration techniques.

The variables analyzed included the following:

- Demographic data: patient age, gender, type and origin.
- Origin of sepsis.

Table 1 Organ and system dysfunctions secondary to sepsis.

- Respiratory: lung infiltrates and hypoxemia with $\text{PaO}_2/\text{FiO}_2 < 300$ mmHg
- Oliguria (diuresis < 0.5 ml/kg/h during at least 2 h)
- Creatinine > 2 mg/dl or increase > 0.5 mg/dl
- Coagulopathy (INR > 1.5 or aPTT > 60 s)
- Thrombocytopenia $< 100,000/\text{mm}^3$
- Hyperbilirubinemia (bilirubin > 2 mg/dl)
- Hyperlactacidemia (> 3 mmol/l or 24 mg/dl)
- Hypotension (systolic blood pressure < 90 mmHg, mean blood pressure < 70 or drop in systolic blood pressure > 40 mmHg)

- Severity data: APACHE II score (in all patients except those who died within the first 24 h after admission to the ICU), organ dysfunction secondary to sepsis and manifesting in the first 24 h (Table 1), peak procalcitonin (PCT) values (included in the database from June 2008, with 100 ng/ml as the maximum value offered by the laboratory) and lactate (where requested) in the first 6 h after admission to the ICU. Since January 2009 we include lactate 24 h after admission to the ICU.
- Management data (in many cases, the initial resuscitation measures recommended in the SSC guides were started outside our Unit, and even outside our hospital, and precise information on these measures was lacking in some instances; for this reason we only refer to the measures adopted in the first 24 h, in the ICU): measurement of central venous pressure (CVP), use of vasopressors, corticosteroids and activated protein C, blood glucose curve, presence of hypoglycemia, and the need for MV and extracorporeal filtration techniques. The use of antibiotic treatment prior to admission to the ICU was registered, along with possible blood cultures obtained before or upon admission to the ICU.
- Mortality and days of stay in the ICU, and total hospital stay.

Statistical analysis

The quantitative variables are expressed as mean and standard deviation, while the qualitative variables are reported as absolute frequency and percentage. The comparison of means was based on the Student's *t*-test or analysis of variance (ANOVA), while the comparison of proportions was carried out using the chi-squared test. Statistical significance was accepted for $p < 0.05$. The SPSS version 11 statistical package was used throughout. Multivariate analysis was based on the construction of a logistic regression model using the stepwise-backwards approach. The goodness of fit of the model was evaluated with the Hosmer–Lemeshow test.

Results

A total of 6263 patients were admitted to our Unit during the study period. Of these, 511 presented septic shock/severe sepsis upon admission or developed septic shock/severe

Table 2 Characteristics of the patients with severe sepsis/septic shock.

	No (%)	Standard deviation
<i>Total septic patients</i>	511 (100)	
<i>Mean age</i>	63	14.4
<i>APACHE II</i>	21	7.6
<i>Male gender</i>	340 (66.5)	
<i>Type of patient</i>		
Medical	348 (68)	
Emergency surgery	89 (17)	
Programmed surgery	63 (12)	
Trauma	11 (2)	
<i>Origin</i>		
Donostia Hospital ward	206 (40.5)	
Ward of other hospital	67 (13)	
Emergency Department	190 (37)	
ICU	48 (9.5)	
<i>Origin of sepsis</i>		
Pneumonia	124 (24)	
Intraabdominal infection	114 (22)	
UTI	69 (13)	
Unknown	51 (10)	
Biliary tract infection	39 (8)	
Soft tissues	40 (8)	
Catheter	26 (5)	
Endocarditis	13 (3)	
Others	35 (7)	
Septic shock	374 (73)	
Severe sepsis	137 (27)	
<i>Organ and system dysfunction</i>		
Respiratory	294 (57.5)	
Oliguria	381 (75)	
Creatinine elevation	351 (69)	
Coagulopathy	202 (39.5)	
Thrombopenia	179 (35)	
Hyperbilirubinemia	109 (21)	
Hyperlactacidemia	226 (44)	
Hypotension	469 (92)	
<i>Stay (days)</i>		
Mean ICU	14	13.7
Median	8	
Mean hospital	38	40.5
Median	25	
<i>Mortality n (%)</i>		
In-ICU	106 (20.8)	
In-hospital	137 (27)	

sepsis during their stay in the ICU (8% of all admissions). On considering only the non-coronary patients (2880 patients), this percentage reached 18%.

As can be seen in Table 2, there was a clear predominance of males among the septic patients (66.5%). The mean age was 63 years, and the mean APACHE II score was 21. The great majority of patients were medical cases (68%), followed by emergency surgery cases (17%) and programmed surgery cases (12%). There were 11 trauma patients (2%). Over one-half of the patients (53.5%) were admitted from

ward areas (40.5% in our hospital and 13% in other centers), 37% were admitted directly from the Emergency Department, and 9.5% suffered the sepsis episode during admission to the ICU. Regarding the origin of sepsis, pneumonia was the most frequent cause (24% of the patients), followed by intraabdominal infections (22%) and urinary tract infections (UTIs) (13%). Sepsis was of unknown origin in 10% of the cases. The percentage of biliary tract and soft tissue infections was similar (8%). Severe catheter-related sepsis was recorded in 5% of the cases. Thirteen patients (3%) presented endocarditis. In the rest of the cases (7%) the causes were very diverse (meningitis, mediastinitis, gastroenteritis, leptospirosis, etc.). The form of presentation was septic shock in 73% (374 patients), and severe sepsis in 27% (137 patients). Arterial hypotension and kidney disorders were the most frequent organ dysfunctions, followed by respiratory disease.

Regarding clinical management, we recorded the PCT values in 442 patients with a mean value of 33.5 ng/ml. Lactate in the first 6 h was requested in 77% of the patients, with a mean value of 27 mg/dl. In 56% of the cases we registered the lactate concentration after 24 h, with a mean value of 30 mg/dl.

A total of 418 patients (82%) had received some antibiotic dose before admission to the ICU. Blood cultures were requested before admission or upon admission to the ICU in 461 patients (90%), and in 47% of the cases some microorganism was isolated. Noradrenalin was used as vasopressor in all cases of shock. In a total of 250 patients (49%), the recorded CVP was ≥ 8 mmHg. In turn, the blood glucose curve was recorded in 479 patients (94%), though only 247 patients (43%) yielded a median blood glucose concentration of <150 mg/dl. Hypoglycemia was observed in 64 patients (12.5%). Corticosteroids were used in 349 patients (68%) and activated protein C in only 10 patients (2%). Over one-half of the patients (277) needed MV (54%), and one-third (33%) required continuous veno-venous hemofiltration (CVVH).

The mortality rate in the ICU was 20.8% (106 patients) (6.6% in the patients with severe sepsis and 25.9% in the cases of shock), while the in-hospital mortality rate was 27% (137 patients). The mean stay in the ICU was 14 days, with a median of 8, and the mean total hospital stay was 38 days with a median of 25.

In reference to the deceased patients, the univariate analysis (Tables 3 and 4) showed the APACHE II scores and the PCT and lactate values to be significantly higher after both 6 and 24 h. Percentage organ or system involvement was also higher, with the exception of hypotension. The patients admitted from ward areas and those who developed sepsis in the ICU showed higher mortality. In relation to the etiology of sepsis, the highest mortality rates corresponded to sepsis of unknown origin and of intraabdominal origin, while in contrast the highest survival rates corresponded to catheter-related sepsis and especially sepsis of urinary origin. The requirements in terms of MV and CVVH, and the percentage of hypoglycemia, were significantly greater among the patients who died. Of all these factors, the multivariate analysis (Table 5) showed mortality to be mainly influenced by the presence of hypoglycemia, respiratory disorders, the need for MV, hyperlactacidemia, thrombocytopenia and an in-hospital or in-ICU origin of the patient.

Table 3 Comparative analysis of the quantitative variables in relation to mortality.

Condition at discharge ICU	No.	Mean (SD)	<i>p</i>
<i>APACHE II</i>			
Deceased	95	26.35 (8.2)	0.05
Alive	405	19.81 (6.8)	
<i>Age</i>			
Deceased	106	65.3 (13.9)	0.090
Alive	405	62.7 (13.4)	
<i>Procalcitonin (ng/ml)</i>			
Deceased	92	41.60 (39.2)	<0.001
Alive	350	31.37 (32.8)	
<i>Lactate 6 h (mg/dl)</i>			
Deceased	91	42 (30)	<0.001
Alive	305	23 (14.6)	
<i>Lactate 24 h (mg/dl)</i>			
Deceased	63	54 (42.4)	<0.001
Alive	227	23.5 (15.8)	
<i>Median blood glucose (mg/dl)</i>			
Deceased	98	146 (51.8)	0.971
Alive	381	162 (57.2)	

SD, standard deviation.

Discussion

Severe sepsis remains a frequent problem, affecting 12–34% of all patients in the ICU, and with an associated mortality rate of between 27 and 35%.^{6–10} In our series, 18% of the patients presented severe sepsis or septic shock upon admission to or in the course of admission to the ICU.

On comparing our data with those obtained in the Edu-sepsis study, patient age and the APACHE II score were found to be similar, and although with somewhat different percentages, most of the patients were males, medical cases, and were mostly admitted from ward areas. The most frequent origin of sepsis was pneumonia, followed by intraabdominal infections, and urinary sepsis. Of note in our series is the large proportion of cases of sepsis of unknown origin (10%), which was slightly higher than the values found in other registries.^{9,11} As regards organ or system involvement, our data coincide with those of the national survey–hemodynamic alterations being the most frequent presentation, followed by renal and respiratory disorders.

In a number of trials, the detection of PCT has been confirmed as a sepsis marker in severe infection; concentrations of >10 ng/ml are associated to multiorgan failure (MOF), and although there is controversy over the issue, PCT has been found to be a prognostic marker.^{12,13} Likewise, the magnitude of lactacidemia reflects the severity of hypoperfusion and is directly related to mortality. Septic patients with early lactate elevation, particularly above 24 mg/dl, have a poorer prognosis, and persistently elevated values (over 24 h) have been associated with mortality rates of up to 89%.^{14–16} Compared with the survivors, the patients who died in our registry had significantly higher PCT (42 vs 31 ng/ml), lactate concentrations in the first 6 h (42 vs 23 mg/dl), and especially lactate concentrations after 24 h

Table 4 Comparative analysis of the qualitative variables in relation to mortality.

	Deceased in-ICU No. (%)	Alive No. (%)	<i>p</i>
Gender			
<i>M</i>	67 (19.7%)	273 (80.3%)	0.415
<i>F</i>	39 (22.9%)	132 (77.1%)	
Type of patient			
<i>Medical</i>	63 (18.1%)	282 (81.9%)	0.015
<i>Trauma</i>	5 (45.5%)	6 (54.5%)	
<i>Emergency surgery</i>	26 (29.2%)	63 (70.8%)	
<i>Programmed surgery</i>	12 (19%)	51 (81%)	
Origin			
<i>Emergency Department</i>	31 (16.4%)	159 (83.6%)	0.024
<i>Donostia Hospital ward</i>	49 (23.8%)	157 (76.2%)	
<i>Ward of other hospital</i>	10 (14.9%)	57 (85.1%)	
<i>ICU</i>	16 (33.3%)	32 (66.7%)	
Origin of sepsis			
<i>Unknown</i>	17 (33.3%)	34 (66.7%)	0.039
<i>Intraabdominal</i>	32 (28.1%)	82 (71.9%)	
<i>Endocarditis</i>	3 (23.1%)	10 (76.9%)	<0.001
<i>Pneumonia</i>	26 (21%)	98 (79%)	
<i>Cholecystitis/cholangitis</i>	7 (17.9%)	32 (82.1%)	0.013
<i>Soft tissues</i>	7 (17.5%)	33 (82.5%)	0.008
<i>Catheter</i>	2 (8.7%)	24 (91.3%)	
<i>UTI</i>	5 (7.2%)	64 (92.8%)	<0.001
<i>Others</i>	7 (18.9%)	28 (81.1%)	
Organ and system dysfunctions			
<i>Respiratory</i>			<0.001
No	23 (10.6%)	195 (89.4%)	
Yes	83 (28.3%)	210 (71.7%)	
<i>Oliguria</i>			0.012
No	17 (13.1%)	114 (86.9%)	
Yes	89 (23.4%)	291 (76.6%)	
<i>Creatinine elevation</i>			<0.001
No	22 (13.8%)	139 (86.3%)	
Yes	84 (24%)	266 (76%)	
<i>Coagulopathy</i>			0.140
No	43 (14.0%)	266 (86%)	
Yes	63 (31.2%)	139 (68.8%)	
<i>Thrombocytopenia</i>			
No	53 (16.0%)	280 (84%)	
Yes	53 (29.8%)	125 (70.2%)	
<i>Hyperbilirubinemia</i>			
No	74 (18.4%)	329 (81.6%)	
Yes	32 (29.6%)	76 (70.4%)	
<i>Hyperlactacidemia</i>			
No	28 (9.9%)	257 (90.1%)	
Yes	78 (34.5%)	148 (65.5%)	
<i>Hypotension</i>			
No	5 (12.2%)	36 (87.8%)	
Yes	101 (21.5%)	369 (78.5%)	
Type			
<i>Severe sepsis</i>	9 (6.6%)	127 (93.4%)	<0.001
<i>Septic shock</i>	97 (25.9%)	278 (74.1%)	
Antibiotics before ICU			
<i>No</i>	22 (23.7%)	71 (76.3%)	0.444
<i>Yes</i>	84 (20.1%)	334 (79.9%)	

Table 4 (Continued)

	Deceased in-ICU No. (%)	Alive No. (%)	<i>p</i>
<i>Positive blood cultures</i>			
No	55 (19%)	236 (81%)	0.256
Yes	51 (23.2%)	169 (76.8%)	
<i>CVP ≥ 8</i>			
No	55 (21.2%)	206 (21.2%)	0.869
Yes	51 (20.5%)	198 (79.5%)	
<i>Corticosteroids</i>			
No	22 (13.6%)	140 (86.4%)	0.007
Yes	84 (24.1%)	265 (75.9%)	
<i>Activated protein C</i>			
No	103 (20.6%)	398 (79.4%)	0.466
Yes	3 (30%)	7 (70%)	
<i>Hypoglycemia</i>			
No	74 (16.6%)	373 (83.4%)	<0.001
Yes	32 (50%)	32 (50%)	
<i>MV</i>			
No	17 (7.2%)	219 (92.8%)	<0.001
Yes	89 (32.4%)	186 (67.6%)	
<i>CVVH</i>			
No	48 (14.1%)	293 (85.9%)	<0.001
Yes	58 (34.1%)	112 (65.9%)	

(54 vs 23.5 mg/dl). Furthermore, the multivariate analysis identified the presence of hyperlactacidemia as one of the variables associated to mortality. As can be seen, among the survivors, the mean lactate levels after both 6 and 24 h remained under 24 mg/dl.

Regarding organ involvement, and in coincidence with other studies,^{9,10,17} percentage organ dysfunction was significantly higher among the patients who died. As shown by the multivariate analysis, in our series the presence of hypoglycemia, respiratory disorders, the need for MV and thrombocytopenia were the alterations most clearly related to mortality. It should be mentioned that we initially used subcutaneous insulin for blood glucose control; as a result, in our patients, hypoglycemia usually reflected liver dysfunction, and was rarely secondary to insulin therapy.

As also evidenced by other publications,^{9,10,18} in our series an in-hospital origin of the patients admitted to the ICU and sepsis originating in the ICU were identified in the multivariate analysis as factors related to mortality. It would

be advisable to determine whether this circumstance is attributable to the nosocomial nature of the infections or to the late identification of infection—with the consequent delay in starting treatment. In this context, it is clear that abidance with the different recommendations of the SSC guides is suboptimal. Although the number of blood cultures requested, the measurement of laboratory test parameters (PCT and lactate), and the use of corticosteroids were greater than in the Edu-sepsis study, the percentage obtainment of correct CVP and adequate blood glucose control was low (albeit similar to that reported in the Edu-sepsis study). The percentage use of activated protein C is infrequent in our Unit (2%), and is even lower than the national average (5–6%).

Many studies have confirmed a decrease in mortality with the early administration of appropriate antibiotic treatment.^{19–21} In our case, on comparing the deceased patients vs the survivors, no significant differences were found in the percentage of individuals who had received

Table 5 Multivariate analysis of the variables associated to mortality. Final model.

Parameters	Odds ratio	Confidence interval (95%)	<i>p</i>
Respiratory dysfunction	2.978	1.598–5.549	0.001
Creatinine elevation	1.630	0.898–2.957	0.108
Coagulopathy	1.677	0.974–2.888	0.062
Thrombocytopenia	1.712	0.999–2.934	0.050
Hyperlactacidemia	2.678	1.507–4.757	0.001
Type of sepsis	2.019	0.897–4.543	0.089
Hypoglycemia	3.469	1.755–6.857	0.000
MV	3.370	1.780–6.378	0.000
Donostia hospital ward + ICU	2.187	1.284–3.725	0.004

antibiotic treatment before admission to the ICU – though it must be noted that we did not analyze administration time or whether the antibiotic was appropriate in the light of the microbiological findings. Likewise, there were no significant differences between the groups in terms of the number of positive blood cultures.

Lastly, both our in-ICU (20.8%) and in-hospital mortality rates (27%) were lower than in other national studies.^{3,9,11,22} On the other hand, mean patient stay, and especially hospital stay, was longer than in other series—a situation which may be explained in part by the availability in our center of a long-stay unit and the fact that follow-up in all cases was maintained until hospital discharge.

In conclusion, severe sepsis is a frequent disorder in our Unit, with important associated morbidity–mortality. The epidemiological and clinical characteristics of our patients are quite similar to those described in other studies, especially in the Spanish national setting. The presence of hypoglycemia, respiratory dysfunction with the need for MV, and the existence of hyperlactacidemia in the first 24 h have been related to a poorer prognosis among our patients. It is clear that there is room for improvement in patient management. In this sense, as reported by some working groups,²³ it would be advisable to adopt consensus-based and multidisciplinary measures among different hospital Departments, using the same protocols in order to shorten intervention time as far as possible and optimize patient treatment.

Conflicts of interest

The authors declare no conflicts of interest.

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