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ORIGINAL ARTICLE

Practice in evaluating solid organ transplant candidates and recipients with neurological impairment: The European Academy of Neurology neurocritical care panel survey

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Abstract

Background: Brain disorders can occur in the context of peripheral organ diseases as well as solid organ transplants. The aim of this study was to explore the involvement of neurologists in the evaluation and management of solid organ transplant candidates and recipients when a nervous system impairment co-exists.

Methods: We invited all European Academy of Neurology members to answer a web-based survey. Descriptive statistics were used to summarize the results.

Results: In total, 176 respondents completed the survey; neurologists are more involved in the evaluation of neurological complications after (31.8%) than before an organ transplant (21%), when they see a small volume of patients, and mainly for neurological comorbidities. A minority (9%) of neurologists received a specific training on the topic of neurological manifestations of extracranial conditions as well as only 6.2% of them are involved in research activities in the brain–body interactions field.

Conclusion: This survey highlights a mismatch between the impressive statistics on brain dysfunction in peripheral organ diseases as well as transplant and the small volume of solid organ transplant candidates/recipients seen by neurologists. According to recent recommendations every organ-eligible candidates should undergo a cognitive screening, however, it is not common that neurologists are involved in the multidisciplinary committee to determine the transplant eligibility. Delirium is the most frequent reason for a neurological consultation after a transplant, but also other critical brain conditions. Educational programs in the field of neurology of systemic diseases are worth being implemented as well as including neurologists in research programs on brain–body interactions.

KEYWORDS
brain dysfunction, brain–body axis, cognition, solid organ transplant, systemic mechanisms

BACKGROUND

Brain disorders commonly occur in the context of or as a consequence of an underlying disease affecting a peripheral vital organ (liver, kidney, pancreas, heart, lung) [1]. Neurological impairment in the setting of a prevailing extracranial disease can be organ-specific (e.g., hepatic encephalopathy in liver failure) or common to any systemic condition causing metabolic derangements or requiring potentially neurotoxic medications (e.g., symptomatic seizures or encephalopathy) [reviewed in Continuum issues 2023, 2020, 2017, 2014 "Neurology of systemic disease"]. Nervous system impairment as a result of systemic disease is obviously more probable in the end-stage phases of the extracranial disease when a patient is evaluated as a recipient for organ transplant. Moreover, among patients receiving solid organ transplants (SOT), approximately one-third will develop neurological complications [2], with a broad range of neurological symptoms/signs/syndromes. Neurologic complications of organ transplantation may be divided into complications common to all types of allografts, mainly related to immunosuppressant drugs, and complications relatively specific to a particular type of organ transplantation (e.g., central pontine myelinolysis in liver transplant) [3].

Since the prevalence of older adults with organ failure is increasing, it is becoming common to waitlist and transplant patients aged 65 years and older [4]. Therefore, over the coming years, neurologists can be expected to consult more frequently with older adults who are potential organ transplant candidates and who have a neurological age-related disease, mainly causing cognitive impairment. In a healthcare system with limited resources, the process of managing access to organs for transplantation in cognitively impaired people is extremely challenging, and so, thus far, this clinical topic has been addressed as an ethical challenge [5].

We are pleased to acknowledge that the most recently updated heart transplant guidelines include a paragraph on the management of neurological complications [6]; however, other SOT guidelines on neurological complications are either dated (e.g., for liver) [7] or missing (e.g., kidney) [8, 9].

Considering the high volume of neurological complications or comorbidities in SOT candidates/recipients, we designed a survey guided by the European Academy of Neurology (EAN), with the aim of exploring: (i) Whether neurologists are involved in the evaluation of SOT candidates and recipients and under which circumstances they are consulted; (ii) whether neurologists are involved in multidisciplinary discussions on transplant eligibility after having evaluated SOT candidates with neurological impairments; (iii) whether neurologists receive specific training during residency and whether they are involved in any ongoing research projects in the field of neurology of systemic diseases and/or solid organ transplant.

METHODS

After a series of correspondence emails between the survey's proponents (VLR, FA, ELG, MP), the EAN Scientific Committee delegate (ML), and a co-chair of the Neurocritical Care Panel (GF), the questions to be included in a web-based survey (Survey Monkey Momentive Europe UC—Dublin, Ireland) were defined. The final survey design included three main sections: (i). Demographics of survey participants (target: neurologists). (ii). Characteristics of their practice consulting pre-transplant candidates. (iii). Characteristics of their practice consulting post-transplant recipients. Two more specific questions were included to explore training experience and research activities in the field of neurology of systemic diseases. The team also approved the text of the email introducing the purpose of the survey (Appendix S1). The survey was approved by the Institutional Research Review Board (IRRB) of the Scientific Institute for Research, Hospitalization and Healthcare (IRCCS)—Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT) with the number IRRB/27/24. Since the study did not include any patient-related data but instead focused on collecting general information from neurologists' practices, no ethical approval was needed according to the rules of the local Ethics Committee. The participants gave electronic informed consent to participate in the survey after reading the Data protection, privacy compliance, and contact information paragraph. The study was performed in accordance with the Declaration of Helsinki and followed the current European regulations for data protection.

The survey was launched on June 7, 2024, via an email sent by the EAN Scientific Office to a total of 3547 EAN members, inviting them to respond within a month. During the time the survey was open, all survey proponents advertised the initiative among their local, national, and international contacts in order to increase the number of participants. During the EAN annual meeting held in July 2024 in Helsinki, VLR was invited to present the ongoing survey to other members of the Neurocritical Care Scientific Panel during the business session; moreover, during the same international meeting, VLR and the EAN Scientific Office delegate (ML) decided to extend the survey deadline until July 24 in order to allow more participants to take part and to obtain more reliable results.

Statistical analysis: Qualitative variables were described by percentages and frequency distributions, while quantitative variables were expressed as means ± standard deviations (SD) or medians ± interquartile ranges. Data distribution of quantitative variables was assessed using the Kolmogorov–Smirnov test. Boxplots and barplots were used to graphically represent the distribution of the data (Appendix S2). All statistical analyses were performed using R version 4.4.1 (The R Society, Auckland, New Zealand) and Microsoft Excel 2013 (Microsoft, Redmond, WA, USA).

TABLE 1 Sociodemographic and professional information of the EAN Scientific Panel NeuroCritical Care's Survey participants.

Demographic Features		Missing data
Age in years, mean (SD)	43.63 (13.35)	21/176 (11.93%)
Gender, male/female/other, *n* (%)	93/63/1 (52.84/35.80/0.57)	19/176 (10.80%)
Years in clinical practice, *n* (%)		
Resident	29 (16.48)	19/176 (10.80%)
Junior consultant (0–4 years)	38 (21.59)	
Consultant (5–9)	18 (10.23)	
Senior consultant (10–19 years)	28 (15.91)	
>20 years	44 (25)	
Primary work setting[a], *n* (%)		
Public Hospital	54 (30.68)	2/176 (1.13%)
University Hospital	89 (50.57)	
Private Hospital	25 (14.20)	
Research facility	19 (10.80)	
Outpatient service	17 (9.66)	
Private practice	13 (7.39)	
Other	1 (0.57)	
Neurology practice main focus[a], *n* (%)		
Consultation Service	93 (52.8)	19/176 (10.8)
Ward Service	74 (42)	
Neurointensive care unit/Emergency neurology	70 (39.8)	
Stroke Service	69 (39.2)	
Clinical neurophysiology/Epilepsy	49 (27.8)	
Neurorehabilitation	11 (6.3)	

Note: The table 1 describes sociodemographic and professional information of the neurologists who participated to the survey: they were represented by professionals of any stage of a career path (from residency to more than 20 years in practice), mostly working at university hospitals (50.5%) and public hospitals (30.6%). We listed the 6 most frequent subspecialties as the main focus of our participants' work (consultation service, ward service, neurointensive care unit/emergency neurology, stroke service, clinical neurophysiology, and neurorehabilitation), however, a full list of our neurologists' focus is available in Appendix S2.

Abbreviations: EAN, European Academy of Neurology; n, number; SD, Standard Deviation.

[a]More than one answer was allowed.

RESULTS

The total number of neurologists who responded to the survey was 176, with a completion rate of 68%. Of these 35.8% were female, the mean age was 43.6 years (standard deviation, SD 13.35), and they were quite homogeneously distributed across all the different stages of their career pathways, from residency to senior practice (more detailed sociodemographic and professional features of the survey participants are reported in Table 1). A final number of 174 responses were considered in the analysis since 2 people declined the consent approval for data sharing. A geographic map depicting the worldwide distribution of the respondents' neurology practice locations is shown in Figure 1. Most of our respondents were located in Western European countries (46%), Central Europe was also represented by 14.2% of all participants, only 5.68% were located in an Eastern European country, and finally, we had participants from non-European countries (18.75%) and World Health Organization (WHO) countries (3.9%) (a more detailed description on Countries classification is available in Appendix S2).

All colored countries represent the locations of the respondents' neurological practices; different colors are associated with a different range in the number of responses obtained. Most of our respondents were located in Portugal and Italy, followed by neurologists practicing in France, Germany, India, Poland, Austria, Belgium, Brazil, Turkey, and Ukraine.

Almost half of the neurologists surveyed (52.8%) work in a consultation service, which is probably the neurology service most involved in the evaluation of SOT candidates and recipients admitted and managed in non-neurological settings.

Though around 43% of neurologists affirmed that SOT programs are active in the same or an affiliated hospital where their neurology practice takes place, only 21% of them are involved in the evaluation of SOT candidates as part of their current activity, and mainly with a low patient volume over a year (less than 20

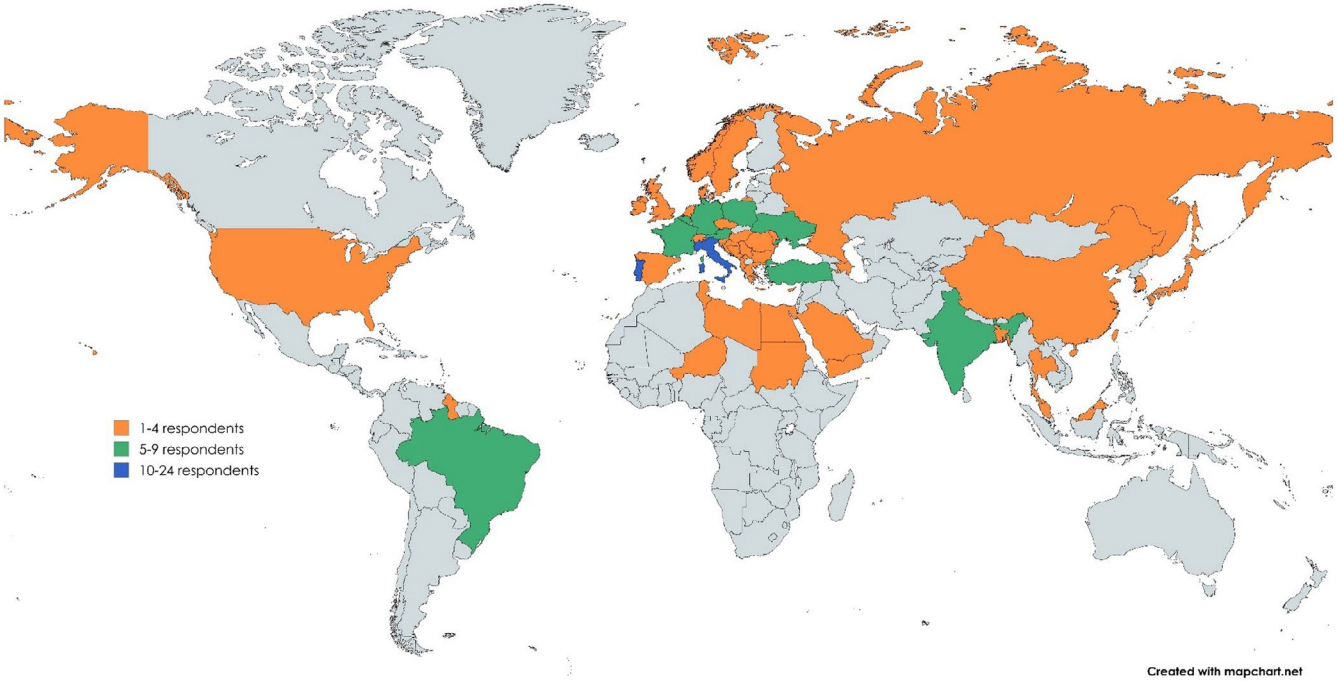

FIGURE 1 Geographic map representing the countries where the neurology practices of the survey participants are located.

patients/year for 76.3% of them) (see Table 2 and Appendix S2 for more details).

The frequency of SOT candidates seen by neurologists when divided according to peripheral organ disease (Table 2) reproduces the frequency of organ transplant types worldwide (https://www.transplant-observatory.org/), except for liver transplant candidates: though kidney transplantation is much more frequent (102,090 worldwide in 2022) than liver transplant (37,436 worldwide in 2022), liver transplant candidates are more frequently evaluated by neurologists than kidney transplant candidates (14.77% vs. 13.64%), probably because of hepatic encephalopathy.

The most frequent reasons neurologists are consulted for SOT candidates are the following: (i) if patients have a neurological comorbidity not correlated with the preeminent vital organ disease (44.89%); (ii) if patients are affected by a neurological complication correlated with the predominant vital organ disease (32.39%); (iii) if cognitive screening is indicated (23.30%); (iv) if brain neuroimaging, included in the diagnostic work-up to determine transplant eligibility, has to be interpreted (24.43%); (v) other reasons (17%). The Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment Test (MoCA) test are equally used (45.4% and 46% respectively) as cognitive screening tools during the clinical practice of the survey participants.

Finally, only 17.5% of neurologists reported being involved in the multidisciplinary discussion on transplant eligibility of an SOT candidate after having evaluated the patient for neurological impairment.

The third part of the survey was dedicated to exploring whether neurologists in their practice are consulted by transplant teams when acute or chronic neurological complications occur in SOT recipients. We found that 31.82% of neurologists are involved in the evaluation and management of patients with an acute neurological complication occurring soon after SOT, with delirium/encephalopathy being the most frequent neurological complication (26.7%). A full list of neurological complications seen by neurologists after SOT is shown in Figure 2.

The graph shows the frequency of reasons for neurological consultation after SOT: as expected, encephalopathy/delirium/acute mental status change (26.7%) is the most frequent neurological complication, followed by symptomatic seizures (17%), neurotoxicity (mainly by calcineurin inhibitors) and acute cerebrovascular disease (each 14.2%); then neuroinfections (9.1%), posterior reversible encephalopathy (8%), peripheral nerve injuries (5.1%), and central pontine myelinolysis (3.4%).

Not only are neurologists consulted during the perioperative period for acute neurological complications after SOT, but 33% of them see SOT recipients in an outpatient setting for long-term neurological signs/symptoms.

Only 9% of neurologists reported receiving specific training on neurological manifestations of extracranial conditions, including solid organ transplant, during residency. Lastly, only 6.2% of neurologists are involved in research activities in the fields of neurology of systemic disease and/or neurology of solid organ transplant or brain–body interactions.

CONCLUSION

Neurologists, in their clinical practice (mainly consultation services), may encounter patients with neurological signs and symptoms that overlap a vital organ disease both as a neurological

TABLE 2 Neurology practice in the evaluation of SOT candidates.

SOT candidates' volume range seen by neurologists over a year, *n* (%)	
<20	29 (76.3)
20–50	5 (13.2)
50–100	1 (2.6)
>100	3 (7.9)
Kind of SOT candidates seen by neurologists, *n* (%)	
Liver	26 (14.77)
Kidney	24 (13.64)
Combined	19 (10.8)
Heart	18 (10.23)
Lung	11 (6.25)
Pancreas	6 (3.41)
Other	3 (1.70)
Circumstances in which neurologists see SOT candidates, *n* (%)	
Neurological comorbidity[a]	79 (44.89)
Neurological complication[b]	57 (32.39)
Brain imaging interpretation	43 (24.43)
Cognitive screening	41 (23.30)
Other reasons	30 (17.05)

Note: Most of neurologists involved in the evaluation of SOT candidates see a low volume of patients in a year (less than 20 patients/year for 76.3% of neurologists); neurologists are mainly consulted for liver (14.7%) and kidney (13.64%) transplant candidates; neurological comorbidities (44.89%) and neurological complications (32.39%) are the most frequent circumstances when neurologists are consulted for SOT candidates.

Abbreviation: n, number.

[a]Neurological comorbidity: brain injury not correlated with the preeminent vital organ disease.

[b]Neurological complication: brain injury correlated with the predominant vital organ disease.

comorbidity or complication [10]. To give a few examples related to different vital organ diseases, patients affected with heart failure can present with thromboembolic stroke, global cerebral hypoperfusion, and cognitive impairment [11]; similarly, neurological effects of prolonged or severe hypoxia in lung disease may lead to encephalopathy, coma, or polyneuropathy [11]; the newly defined concept of the kidney-brain axis includes all the neurological manifestations that occur in chronic kidney disease [12]; a broader range of central nervous system impairments can occur in the context of liver disease, both acute and chronic, including hepatic encephalopathy and acquired hepatocerebral degeneration [13]; and neuromuscular complications in diabetes mellitus are well known [14]. Lastly, since SOT candidates are increasingly older [15], it is expected they may have a larger burden of comorbidities, including age-related neurological diseases, mainly neurodegenerative disorders and cerebrovascular disease [16]. Despite this big overlap between a peripheral organ disease and nervous system functioning, according to the EAN Neurocritical Care Panel survey, only 1 in 5 neurologists see SOT candidates, though half of them practice in a consultation service and in a hospital where a SOT program is active. Neurologists involved in SOT candidate evaluation see a small number of patients each year, despite data from the Organ Procurement and Transplantation Network (https://www.organdonor.gov/learn/organ-donation-statistics) showing that as of September 2024, 101,912 adult patients were on a waiting list for solid organ transplant in the United States, of whom 26,460 were over 65 years old. Similarly from the Eurotransplant Statistics Report Library, we know that 13,448 persons were on the active waiting list (at year-end) 2023 (https://www.eurotransplant.org/statistics/yearly-statistics/).

Regardless of etiology, it is common that brain impairment, in the context of a prevailing severe extracranial disease, results in cognitive impairment. For example, reported cognitive impairment ranges from 42 to 80% in liver-candidate populations and 10 to 55% in kidney-eligible cohorts [17]. Since organ-eligible candidates carry this higher risk of cognitive impairment beyond normal aging, current guidelines agree that cognitive assessment is an important part of the organ transplantation process [17]; however, only 23.3% of neurologists are involved in the cognitive screening of SOT candidates and even fewer (17.5%) are involved in multidisciplinary discussions on transplant eligibility of an assessed patient. Access to organ transplant for cognitively impaired patients is still a matter of ethical debate [5], as organs are a limited healthcare resource, and it is worth involving neurologists more actively as cognitive impairment specialists. During the transplantation process, neurologists would ensure the standardization of cognition assessment, the definition of the etiological diagnosis of cognitive impairment, and the determination of pharmacological and non-pharmacological interventions, as well as perioperative risks.

A higher percentage of neurologists reported being involved in SOT recipient consultations in the perioperative period, even though they are only expected to see a small selection of those patients, who are often managed by the same transplant team or critical care physicians [18]. Data from the Global Observatory on Donation and Transplantation (https://www.transplant-observatory.org/) show that 157,494 solid organ transplants were performed in 2022, a 9.1% increase from the previous year. It is expected that approximately one-third of patients receiving solid organ transplants will develop neurologic symptoms, most within 30 days of transplantation [2]. Hence, the estimated need for neurological consultation across transplant units is around 52,498 requests per year.

When exploring educational needs in the neurology of systemic diseases, including neurological complications of SOT, we found that less than 1 in 10 neurologists received specific training during residency. This information is relevant to encourage neurologists with this specific expertise to provide educational resources for younger colleagues and stakeholders to include a session on "Neurological issues in the transplantation setting" as an additional learning objective within Section 10 "Neurological manifestations

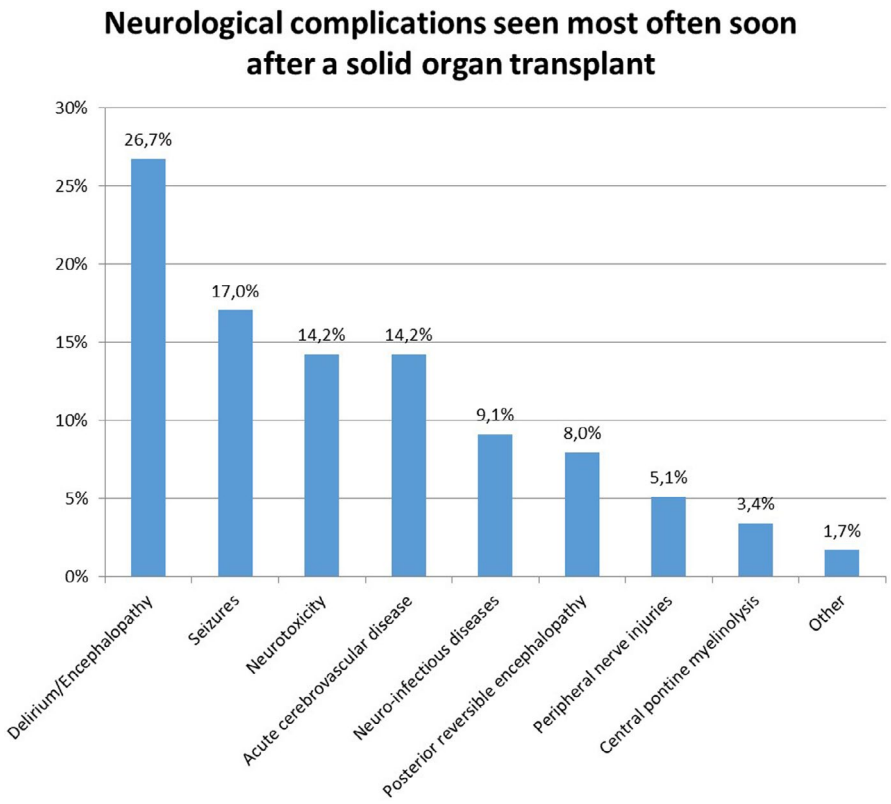

FIGURE 2 Neurological complications as a reason for neurological consultation after solid organ transplant.

and complications of non-primary neurological diseases/conditions and intoxications" in the document entitled European Training Requirements for Neurology (2021).

Lastly, only a small minority of neurologists are involved in research programs in the emerging field of brain–body interactions, which has been the subject of recent funding opportunities (ERA-NET NEURON- The Network of European Funding for Neuroscience Research).

We acknowledge our survey has a major limitation caused by the small number of respondents, most of whom practice in hospitals where transplant programs are not active; on the contrary, we cannot exclude a probable selection bias towards clinicians who have a specific interest in the topic, therefore the educational need provided through our survey may be underestimated. To overcome the limitation of the small number of responses, we are planning to perform a survey targeting healthcare professionals working in transplant hospitals/centers in order to explore if and when a neurological consultation is requested for SOT candidates and recipients. As the additional plan to reach as many neurologists involved in the transplantation field, we aim to involve other international scientific societies in the field of neurocritical care or with an interdisciplinary focus.

The results of our survey are useful to encourage neurologists working in consultation services receiving evaluation requests for SOT candidates and recipients from transplant centers to face multiple clinical needs: a. to provide standard neurological evaluation for SOT candidates with neurological complications or comorbidities (above all cognitive impairment) and work on guidelines for transplant eligibility; b. to provide updates or new guidelines for neurological complications occurring after SOT; c. to supply multidomain interventional programs to preserve brain health before and after the transplant in order to maintain transplant eligibility and then to ensure full compliance with the demanding postoperative immunosuppression regimen and the care required; d. to promote more educational resources for neurology in systemic medical and surgical diseases; e. to implement research programs looking at the mechanisms of nervous system injury caused by peripheral organ dysfunction, as well as how the therapeutic immunosuppressive status of transplant patients influences brain diseases triggered by systemic inflammation [19].

AUTHOR CONTRIBUTIONS

Vincenzina Lo Re: Conceptualization; methodology; formal analysis; supervision; writing – original draft; writing – review and editing. **Giulia Fiume:** Conceptualization; writing – review and editing. **Monica Rizzo:** Writing – review and editing; formal analysis; project administration. **Federica Avorio:** Conceptualization; writing – review and editing. **Maria Lolich:** Methodology; writing – review and editing; data curation; supervision. **Emanuele Lo Gerfo:** Conceptualization; writing – review and editing. **Massimo Pinzani:** Conceptualization; writing – review and editing; supervision. **Antonio Toscano:** Conceptualization; writing – review and editing; supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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