



Effect of Gender and Age on Voriconazole Trough Concentrations in Italian Adult Patients

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Abstract

Background and Objectives The broad-spectrum triazole antifungal agent, voriconazole, is widely used in the treatment of invasive fungal infections. Its treatment efficacy and the occurrence of adverse events are associated with plasma drug concentration, rendering inconsistent or inadequate dosing in many patients. The aim of this study was to evaluate the effect of gender, age, body mass index, ethnicity, serum creatinine and drug dose on voriconazole trough concentration.

Methods A fully validated chromatographic method was used to quantify voriconazole concentration in plasma collected from adult patients at the end of dosing interval. Associations between variables were tested using the Pearson test. The Mann–Whitney *U* test was used to probe the influence of categorical variables on continuous ones.

Results In a cohort of 330 Italian patients treated with voriconazole, males reported a significantly higher drug concentration than females, with values higher than 1000 ng/mL. Moreover, in the univariate analysis, a significant correlation was found between trough concentration and increasing age.

Conclusion Increasing age and gender could influence voriconazole trough concentrations.

Key Points

Inter-individual variability in voriconazole plasma exposure could be the reason of treatment failure or toxicity.

Gender has a significant influence on the voriconazole exposure.

Voriconazole concentration is significantly correlated with age and drug dose.

Screening patient's pharmacokinetic profile may help clinician to optimize voriconazole therapy.

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1 Introduction

The newest generation triazoles, such as voriconazole (VRC), posaconazole and isavuconazole, represent advances in the development of antifungal agents and have been developed to address the increasing invasive fungal infections (IFIs) and the limitations of first-generation agents [1, 2].

VRC (VFendTM; Pfizer Pharmaceuticals), approved by the United States Food and Drug Administration in 2002 was developed to enhance fluconazole potency and spectrum of activity [2]. Effectively, this agent has a broad spectrum of activity and is commonly used for prophylaxis and for IFI treatment [3]. The package leaflet recommends a weight-based intravenous (IV) maintenance dose of 3–4 mg/kg twice daily (b.i.d.) or an oral maintenance dose of 200 mg b.i.d. [4]. However, the selection of the appropriate dose is often based on the nature and severity of the infection. Well-known adverse effects of VRC are hepatotoxicity, visual disturbance and phototoxicity [5]. In patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min),

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accumulation of the intravenous vehicle, sulfobutylether- β -cyclodextrin, occurs. Nevertheless, oral VRC should be administered to these patients, and laboratory evaluation of abnormal renal function is recommended which should include the monitoring of serum creatinine levels. The treatment efficacy and the occurrence of adverse events are associated with plasma drug concentration, highly variable in clinical practice, leading to inconsistent or inadequate dosing in many patients [6]. VRC is metabolized in liver, primarily through cytochrome P450 (CYP) 2C19 and, to a lesser extent, through CYP3A4 and CYP2C9, in inactive metabolites, mainly excreted in urine (80%) [7]. These isozymes are polymorphic thus affect the enzyme activity and influence drug metabolism [8, 9]. VRC has a nonlinear pharmacokinetic, likely the result of saturation of the drug hepatic metabolism [10]. The elimination half-life is approximately 6–9 h for IV and 2–3 h for oral VRC, increasing with increasing dosage [11]. The steady-state of plasma concentrations is obtained after 5–7 days of drug administration [1, 2, 6, 12, 13]. Moreover, its blood exposure is considerable influenced by different factors: increasing age, gender, body mass index (BMI), CYP2C19 polymorphism, liver disease, inflammation and drug interaction [14–17]. For this reason, therapeutic drug monitoring (TDM) is recommended [18].

The optimum VRC trough concentration for clinical response and safety is still controversial [19]. Concerning prophylaxis, the lowest drug exposure cut-off is 1000 ng/mL for efficacy and 4000 ng/mL for toxicity [20, 21]. Considering therapy, those with a VRC plasma concentration > 2000 ng/mL had better clinical response, while patients with > 5500 ng/mL showed a higher risk of drug-related toxicity [21].

Here, we aimed to describe the obtained results from TDM and to investigate the relationship between VRC trough concentration (C_{trough}) and gender, increasing age, BMI, ethnicity, serum creatinine and drug dose, so as to guide VRC individual dosage adjustment.

2 Methods

2.1 Patients and Inclusion Criteria

Plasma samples of patients treated with VRC enrolled at different hospitals in Piedmont (Italy) were collected at the Laboratory of Clinical Pharmacology and Pharmacogenetics (Department of Medical Sciences, Unit of Infectious Diseases, University of Turin, Amedeo di Savoia Hospital, Turin) and at the Clinical Pharmacology Service “Franco Ghezzi” (Department of Biological and Clinical Sciences, University of Turin, S. Luigi Gonzaga Hospital, Turin). Inclusion criteria were: treatment with VRC for IFI prophylaxis or IFI therapy purposes, with an adherence of

90% (self-reported considering oral route of administration and recorded by the nurses for the IV route). Patients on treatment with potential interacting drugs, allergy or intolerance to VRC, HIV infection, severe malnutrition, liver cirrhosis, sepsis, chronic renal failure (with estimated creatinine clearance < 60 mL/min), underlying diagnosis of cancer, undergoing bone marrow or solid organ transplant or immunosuppressed were excluded. The IFI definition is that published by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group [22].

The retrospective study protocol (PkPG_J02AC Studio retrospettivo per la valutazione e farmacocinetica e farmaco-genetica della terapia antimicotica con farmaci triazolici) was approved by the local Ethics Committee. Written informed consent for the study was obtained from each enrolled subject. We obtained only one concentration measurement for each patient. No data successive to dose adjustment have been recorded in this study.

For all the patients, the following data were available: gender, age, BMI, ethnicity, serum creatinine and VRC dose.

2.2 Determination of Voriconazole Plasma Concentration

Blood samples were taken at the end of dosing interval (C_{trough}), before the new dose intake, under steady-state conditions (5 days after both IV and oral administration). Plasma samples were obtained by centrifugation at 3000 rpm for 10 min at 4 °C. The compound, 6, 7-dimethyl-2, 3-di(2-pyridyl) quinoxaline, used as the internal standard and VRC were purchased from Sigma-Aldrich (Milan, Italy). Acetonitrile (HPLC grade) and methanol (HPLC grade) were purchased from VWR (Milan, Italy). Formic acid was from Sigma-Aldrich. HPLC-grade water was produced by a Milli-DI system coupled with a Synergy 185 system by Millipore (Milan, Italy). The full high-performance liquid chromatography coupled to mass spectrometric method for quantification of voriconazole plasma concentration is reported in the Supplementary material [23].

2.3 Statistical Analysis

For descriptive statistics, continuous and non-normal variables were summarized as average, standard deviation (SD), median and interquartile range (IQR), 25th–75th percentiles were calculated to measure the statistical dispersion of the data, while categorical variables were described as frequency and percentage. All the variables were tested for normality with the Shapiro–Wilk test. The correspondence of each parameter was evaluated with a

normal or non-normal distribution, through the Kolmogorov–Smirnov test, to confirm the result obtained with the Shapiro–Wilk test.

The independent samples *t* test was used to compare the means of two independent groups (IV and oral routes of administration), considering the level of statistical significance (*p* value < 0.05) (Table 1). The Pearson linear correlation coefficient (*r*) was used to investigate the strength of the association between two quantitative variables considering the level of statistical significance (*p* value < 0.05). The Mann–Whitney *U* test was used to probe the influence of categorical variables on continuous ones, considering the level of statistical significance (*p* value < 0.05). Any predictive power of the considered variables was finally evaluated through univariate and multivariate linear regression analysis. Factors (β , β coefficient; IC, interval of confidence at 95%) with a *p* value < 0.2 in univariate analysis were included in the multivariate analysis (*p* value < 0.05).

All the tests were performed with IBM SPSS Statistics 22.0 for Windows (Chicago, IL, USA).

3 Results

3.1 Study Population

A total of 371 adult patients were enrolled. The great majority (95.7%; *n* = 355) were Caucasians. A total of 41 (11.05%) received VRC antifungal prophylaxis and have been excluded (Fig. 1). Data and samples from the 330 Italian patients treated with VRC were analysed.

Median and IQR values for age, BMI, creatinine serum levels, VRC dose (mg/kg) and VRC plasma concentration, considering all the cases and those receiving oral and IV administration, have been summarised and are compared in Table 1. For the intravenous route, drug dose and plasma concentration have been evaluated considering pro-kg dosage; In contrast, for oral administration, drug dose and plasma concentration have been evaluated considering the dosage in mg. There were no statistically significant differences in terms of baseline characteristics among the analysed groups.

3.2 Effect of Gender, Age, BMI, Ethnicity, Serum Creatinine and Drug Dose on VRC Concentrations

Concerning all the 330 enrolled patients, a high interindividual variability was found between VRC C_{trough} concentrations: the median value was 1564.5 ng/mL and the IQR range was 539.25 and 3237.0. Among the females, 47.9% reported VRC levels lower than 1000 ng/mL while only 32.6% of males did so; the Mann–Whitney test showed a statistically significant difference (*p* < 0.001).

3.3 Effect of Gender, Age, BMI, Ethnicity, Serum Creatinine and Drug Dose on VRC Concentrations in IV Route of Administration

Table 2 reports the characteristics of male and female patients; significant differences have been observed considering age (*p* = 0.006) and weight (*p* = 0.001).

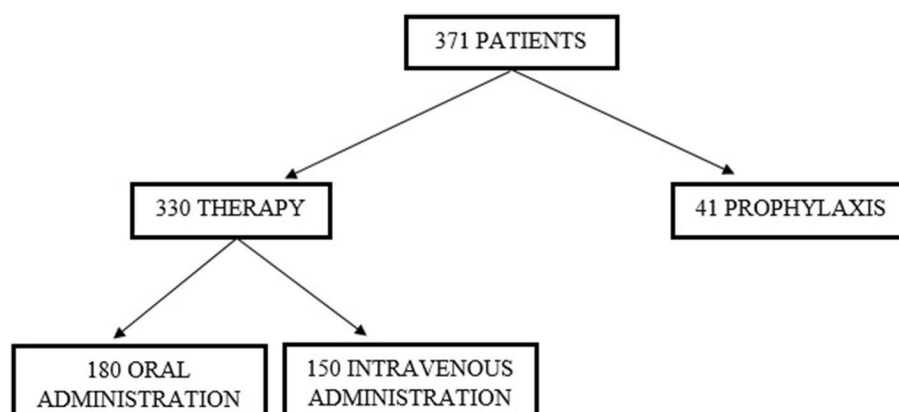
Evaluating those receiving VRC by the IV route (*n* = 150), 109 were males (72.7%). Table 1 reports patient

Table 1 Median and interquartile range for age, weight, body mass index, creatinine serum levels, voriconazole dose and voriconazole plasma concentration, considering oral and intravenous routes of administration

Variable	Intravenous route (<i>n</i> = 150)		Oral route (<i>n</i> = 180)		<i>t</i> test
	Median	IQR	Median	IQR	<i>p</i> value
Age (years)	61.00	52.00–66.00	62.00	50.50–67.00	0.428
Weight (kg)	68.00	57.00–76.50	66.00	57.50–76.00	0.673
BMI (kg/m ²)	23.72	21.10–25.49	22.86	2.033–26.64	0.460
Serum creatinine (mg/dL)	0.78	0.58–1.08	0.88	0.60–1.25	0.248
VRC dose (mg)	–	–	400	400–600	–
VRC dose (mg/kg)	7.92	5.93–9.28	–	–	–
VRC C_{trough} (ng/mL)	2079.00	1123.50–4284.00	1791.00	922.50–3314.50	0.884
VRC C_{trough} /dose (ng/mL/mg)	–	–	3.72	1.82–7.99	–
VRC C_{trough} /dose/weight (ng/mL/mg/kg)	271.44	135.49–617.74	–	–	–

The independent samples *t* test was used to compare the means of two independent groups, considering the level of statistical significance (*p* value < 0.05). For the intravenous route, drug dose and plasma concentration have been evaluated considering pro-kg dosage; in contrast, for oral administration, drug dose and plasma concentration have been evaluated considering the dosage in mg

VRC voriconazole, *n* number, IQR interquartile range, BMI body mass index, C_{trough} concentration at the end of dosing interval, – not evaluated

Fig. 1 Patients' enrollment scheme

characteristics. Performing the Mann–Whitney U test, a statistically significant difference has been reported between genders and VRC concentration/drug dose/kg ($p=0.001$): males reported 353.72 ng/mL/mg/kg (IQR: 180.87–605.21 ng/mL/mg/kg) and females 170.51 mg/kg (IQR: 90.53–321.59 ng/mL/mg/kg) (Fig. 2). Univariate linear regression analysis was performed to evaluate the effect of gender, age and serum creatinine levels on VRC concentrations. Stepwise forward regression analysis was used to identify the minimum set of independent predictive variables of VRC exposure and to estimate the contribution of each factor to pharmacokinetic variability. Age ($p=0.072$; β : 0.148 and IC: -0.443 ; 10.40) and sex ($p=0.123$; β : -0.126 and IC: -275.97 ; 33.40) have been retained in the univariate model, but not in the multivariate analysis, as VRC levels/dose/kg predictors (Table 3). Pearson correlation does not provide statistically significant results.

3.4 Effect of Gender, Age, BMI, Ethnicity, Serum Creatinine and Drug Dose on VRC Concentrations in Oral Route of Administration

Table 2 reports the characteristics of male and female patients and significant differences can be seen considering weight ($p=0.016$) and dose ($p=0.001$).

Considering the group of oral drug administration ($n=180$), 122 were males (67.8%). Table 1 reports patient characteristics. Performing the Mann–Whitney U test, a statistically significant difference has been reported between genders and VRC concentration/drug dose ($p=0.048$): males reported 5.75 ng/mL/mg (IQR: 2.64–11.60 ng/mL/mg) and females 3.31 mg/kg (IQR: 1.82–7.83 mg/mL) (Fig. 3). Univariate linear regression analysis was performed to evaluate the effect of gender, age, BMI and serum creatinine levels on VRC concentrations. Stepwise forward regression analysis was used to identify the minimum set of independent predictive variables of VRC exposure and estimate the contribution of each factor to pharmacokinetic variability. BMI ($p=0.001$; β : -0.246 and IC: -0.644 ; -0.170)

has been retained in the univariate model as VRC levels/dose predictor (Table 3). Pearson correlation does not provide statistically significant results.

4 Discussion

TDM is a well-established and recognized approach for guiding effective and safe therapies in different diseases [24]. VRC has a dose–exposure relationship and its concentration is linked to treatment efficacy and toxicity, supporting a close monitoring during treatment [6]. Furthermore, genetic polymorphisms of the *CYP2C19* gene involved in VRC metabolism could contribute to explaining drug plasma inter-individual variability [15, 25–27]: poor metabolizers have higher concentrations than extensive metabolizers (with at least 1 functional allele) [28, 29]. In poor metabolizers, the CYP3A-mediated pathway is the main drug elimination mechanism, influenced by CYP3A modulators [30]. VRC is also a substrate and/or inhibitor of uridine diphosphate glucuronosyltransferase, transport proteins in the ATP-binding cassette transporter protein family (ABC) and others [31–34]. In addition, the effect of *SLCO1B3*, *ABCG2*, *ABCC2* and *ABCB1* gene polymorphisms on drug pharmacokinetic variability has been demonstrated [35].

In our cohort, highly variable VRC plasma C_{trough} was observed and no significant differences were found in mean concentrations between the evaluated groups (IV and oral administration), supporting that the switch to oral could be made without decreasing plasma concentration [4]. Conversely, another study observed higher trough exposure in those receiving IV drug, explained by the inflammation coinciding with this type of treatment [36].

Considering the gender effect on drug exposure, we observed that males had higher median VRC C_{trough} values than females, evaluating both those receiving IV (Fig. 2) and oral (Fig. 3) VRC. For IV administration, female sex also resulted as a negative predictor of drug plasma levels adjusted for dose/kg (Table 3). These results have been

Table 2 Median and interquartile range for age, weight, body mass index, creatinine serum levels, voriconazole dose and voriconazole plasma concentration, considering oral and intravenous routes of administration, evaluating gender differences

Variable	Intravenous route (n = 150)				Oral route (n = 180)				t test	
	Males (n = 109)		Females (n = 41)		Males (n = 122)		Females (n = 58)		p value	p value
	Median	IQR	Median	IQR	Median	IQR	Median	IQR		
Age (years)	63.00	56.00–68.25	54.00	42.00–61.50	62.00	49.00–65.00	61.00	51.75–69.00	0.006	0.590
Weight (kg)	69.00	61.25–79.75	60.00	51.00–73.50	68.00	60.00–75.00	60.00	51.50–81.25	0.001	0.016
BMI (kg/m ²)	23.69	21.14–25.33	24.22	20.63–26.34	22.65	20.52–25.38	23.35	20.02–32.55	0.965	0.094
Serum creatinine (mg/dL)	0.80	0.61–1.19	0.66	0.55–0.99	0.90	0.62–1.34	0.83	0.56–1.08	0.052	0.271
VRC dose (mg)	–	–	–	–	400	400–400	400	400–700	–	0.001
VRC dose (mg/kg)	7.69	5.82–9.30	8.22	6.67–9.26	–	–	–	–	0.066	–
VRC C _{trough} (ng/mL)	2284.00	1472.75–4434.25	1457.00	382.50–3585.00	1954.00	955.00–3892.00	1547.00	474.75–2775.75	0.073	0.823
VRC C _{trough} /dose (ng/mL/mg)	–	–	–	–	4.53	2.33–10.01	2.68	1.13–4.78	–	0.300
VRC C _{trough} /dose/weight (ng/mL/mg/kg)	325.27	162.21–679.64	166.51	93.49–442.25	–	–	–	–	0.123	–

The independent samples *t* test was used to compare the means of two independent groups, considering the level of statistical significance (*p* value < 0.05); significant values are shown in bold. For the intravenous route, drug dose and plasma concentration have been evaluated considering pro-kg dosage; in contrast, for oral administration, drug dose and plasma concentration have been evaluated considering the dosage in mg

VRC voriconazole, *n* number, IQR interquartile range, BMI body mass index, C_{trough} concentration at the end of dosing interval, – not evaluated

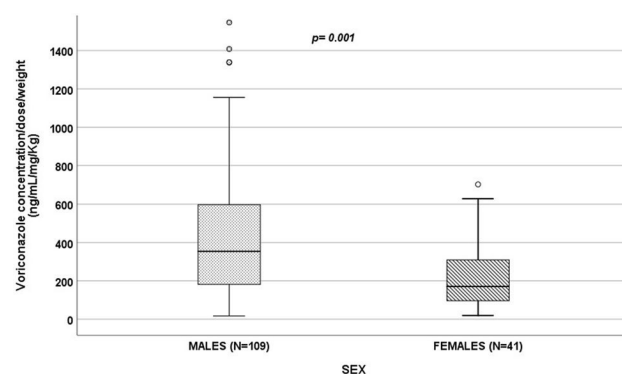


Fig. 2 Gender influence on voriconazole trough concentration/dose/weight, considering patients undergoing intravenous route of administration (*p* = 0.001). Boxes and black lines in boxes represent, respectively, interquartile ranges (IQR) and median values; open dots and stars represent outlier values; whiskers represent highest and lowest values. Males (*n* = 109) had 353.72 ng/mL/mg/kg (IQR: 180.87–605.21 ng/mL/mg/kg) median concentrations; females (*n* = 41) had 170.51 mg/kg (IQR: 90.53–321.59 ng/mL/mg/kg) median concentrations

confirmed evaluating the VRC concentration threshold of 1000 ng/mL, where 47.9% of females had levels lower than 1000 ng/mL, while only 32.6% of males reported suboptimal drug concentrations, a statistically significant result (Mann–Whitney). In addition, using regression analysis, increasing age resulted as a predictive factor of higher VRC C_{trough} in IV routes (Table 3). It is already known that age and sex may also influence VRC levels [37, 38], and a study on healthy volunteers demonstrated that the maximum VRC concentration and area under the curve were higher in elderly male subjects, and in females compared with younger males [39]. A decreased metabolic clearance in the elderly could strongly influence drug concentration, especially considering those renally excreted, such as voriconazole.

In oral administration, which is not prescribed per weight, we observed a predictive role of BMI, in particular that a lower BMI value predicts higher drug concentrations (Table 3); the effect of this factor has been identified in previous studies [40].

Furthermore, a significant difference in drug dose has been reported in all the enrolled patients. These suggested that gender differences could be the result of different doses/kg of body weight. Thus, the recommended weight-based VRC dosing should also consider patient sex to avoid female underexposure.

Gender effect on drug concentrations could be due to sex differences in CYP-mediated metabolism, sexual hormone influence on drug absorption and differences in fat percentage in body composition. Unfortunately, our research is limited by the lack of data regarding female hormonal phase and impedance analysis, not available in a retrospective study.

Table 3 Factors in univariate and multivariate linear regression analyses able to predict voriconazole concentrations at the end of dosing interval C_{trough} , considering intravenous and oral routes of adminis-

tration. Since only body mass index was statistically significant in the univariate analysis, the multivariate analysis has not been performed for the oral route of administration

Factor	Intravenous route		Oral route
	Univariate	Multivariate	Univariate
	<i>p</i> value; β (95% CI)	<i>p</i> value; β (95% CI)	<i>p</i> value; β (95% CI)
Age	0.072; 0.148 (−0.443; 10.400)	0.072; 0.148 (−0.443; 10.400)	0.246; 0.087 (−0.043; 0.167)
Gender	0.123; −0.126 (−275.973; 33.400)	0.239; −0.098 (−252.472; −63.478)	0.300; −0.078 (−4.395; 1.363)
BMI	—	—	0.001; −0.246 (−0.644; −0.170)
Creatinine levels	0.328; 0.098 (−85.151; 252.547)		0.446; 0.072 (−1.006; 2.270)

Significant values are shown in bold

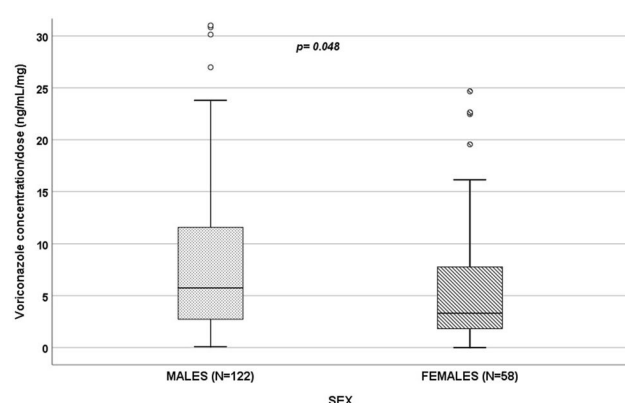


Fig. 3 Gender influence on voriconazole trough concentration/dose, considering patients undergoing oral route of administration ($p=0.048$). Boxes and black lines in boxes represent, respectively, interquartile ranges (IQR) and median values; open dots represent outlier values; whiskers represent highest and lowest values. Males ($n=122$) had 5.75 ng/mL/mg (IQR: 2.64–11.60 ng/mL/mg) median concentrations; females ($n=58$) had 3.31 mg/kg (IQR: 1.82–7.83 mg/mL) median concentrations

Moreover, a decreased metabolic clearance in the elderly could strongly influence drug concentration, especially considering those renally excreted, such as voriconazole.

Since voriconazole is a low aqueous solubility molecule, its IV formulation includes a solubilizing agent, sulfobutylether- β -cyclodextrin sodium, which accumulates in kidneys, leading to reduced renal function [41]. Raised creatinine levels are a marker of drug-impaired renal function. However, in our analysis, no significant correlations have been observed between drug levels and creatinine.

This study has several limitations, such as the retrospective design, the lack of other renal function markers (such as eGFR or similar) and of liver function markers, indications, concurrent medications, a standardized protocol for VRC dosing and of *CYP2C19* variant evaluation, and the limited patient sample size. Further works should be

applied to larger cohorts and include voriconazole pharmacogenetic analysis (such as *CYP* genotyping) are required to confirm our data. Nevertheless, our findings have suggested the effect of increasing age and gender on VRC exposure in the management of antifungal treatment.

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Author Contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by SA, SF, AN, JC, VA, AM, AS and MA. The first draft of the manuscript was written by SA and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Funding No funding has been received for the conduct of this study.

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Comitato Etico Interaziendale A.O.U. San Luigi Gonzaga; reference number PkPG_J02AC) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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