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Gender and age effects on the incidence and severity of chemotherapy-induced neuropathic pain: a propensity score matching analysis

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Abstract

Objective To determine whether the clinical phenotype of chemotherapy-induced neuropathic pain (CINP) varies based on the gender and age of patients.

Methods Retrospective, file-based analysis of cancer patients who received any conventional standard of care chemotherapy and were referred to assess the extent of painful chemotherapy-induced peripheral neurotoxicity (CIPN). A Propensity Score Matching Analysis (PSMA) was conducted to create balanced cohorts; accounting for variables that could impact the incidence and severity of CINP in CIPN patients. A total of 205 males and 295 females were initially included, and after PSMA, 191 patients of each gender were equally matched; totaling 382 patients. These patients were divided according to their age to those aged ≤65 years (group I, *n*=216) and patients aged ≥66 years (group II, *n*=166). CINP was assessed using the pain intensity numerical rating scale (PI-NRS) and the Douleur Neuropathique-4 questionnaire (DN4). The severity of CIPN was graded with Total Neuropathy Score-clinical (TNSc®).

Results The incidence of CINP was similar between males and females (27.2% vs. 27.7%; $p=1$). The same applied for the DN4 scorings at CINP onset (median 7; $p=0.9$). The severity of CINP at the end of chemotherapy, according to PI-NRS, was 7 (range:6–9) for males vs. 7 (range: 5–8) for females ($p=0.09$), while at 3 months post-chemotherapy the PI-NRS scorings were comparable ($p=0.56$). However, males tended towards higher rates of severe CINP (PI-NRS ≥ 7) [males: 59.5%, females: 40.5%; $p=0.1$], compared to female patients, despite having lower CIPN severities, according to TNSc® scoring. No statistically significant differences were observed in the incidence (25% vs. 30.7%; $p=0.214$) and severity (mean PI-NRS difference $p=0.584$) of CINP between age groups. Older male patients presented a higher likelihood (OR: 1.08; 95CI: 1.01–1.16; $p=0.027$) of severe pain (PI-NRS ≥ 7) at the end of chemotherapy, compared to their younger counterparts.

Conclusion There were no significant differences found between the occurrence and severity of CINP, based on gender or age. However, older men had more severe pain raters (PI-NRS), while scoring lower in TNSc® severities.

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Keywords Chemotherapy-induced peripheral neurotoxicity, Chemotherapy-induced neuropathic pain, Gender, Age, Risk factors

Introduction

Exposure to various exogenous neurotoxic sources, including industrial chemical substances in the workplace (occupational hazards) or the environment (environmental hazards), as well as consumption of food, alcohol or drugs, can frequently be associated with acquired toxicity in peripheral nerves [1]. To establish a diagnosis of toxic neuropathy, the following criteria should be fulfilled: (i) subacute onset of peripheral nerve damage; (ii) dose-related progression of symptoms' severity; (iii) evidence for temporal association between neurotoxicity and exposure to a given toxic agent; (iv) exclusion of other causes of peripheral nerve damage, such as metabolic, nutritional and disease-related neuropathies and (v) evidence of improvement once the exposure or treatment ceases, although the phenomenon of coasting, is well described [2, 3]. Coasting stands for continued worsening of neurotoxicity for several months after stopping the treatment, particularly with platinum-based compounds [4].

In developed countries, drug and alcohol-induced neuropathy prevail, while in low-income countries occupational and environmental causes are most commonly seen [5]. Nonetheless, despite the longstanding recognition of toxic drug-induced neuropathies, as a result of exposure to tuberculostatic, anti-arhythmic, anti-retroviral and anti-cancer drugs, particularly chemotherapy-induced peripheral neurotoxicity (CIPN) continue to be a multifaceted and still unresolved clinical issue [6]. Indeed, CIPN accounts for the most significant dose-limiting non-hematological toxicities that can negatively influence the oncological outcome and patients' quality of life [7, 8].

In particular, widely used chemotherapy agents for various common cancer types, including platinum compounds (cisplatin and oxaliplatin), taxanes (paclitaxel and docetaxel), epothilones (ixabepilon), vinca-alkaloids (vincristine), proteasome inhibitors (bortezomib), purine and pyrimidine analogs (nelabarine and clofarabine), and thalidomide, may commonly evoke peripheral nerve damage [9]. However, the clinical issue becomes significant when the effectiveness of these neurotoxic agents cannot outweigh the risk of development of neurotoxicity and CIPN becomes a dose-limiting factor that affect the oncological outcome and patients' quality of life (QoL) [6, 9].

The clinical phenotype of CIPN is mainly comprised of sensory dysfunction with evidence of paresthesias and dysesthesias in peripheral limbs, numbness, tingling, abnormal proprioception, sensory ataxia, and impaired or abolished deep tendon reflexes [10]. CIPN can be painful with the manifestation of burning sensations consistent with neuropathic pain in up to 35% of chemotherapy-exposed patients, as recently demonstrated by our group [11].

The literature contains several reports for modifiable and unmodifiable risk factors predisposing to CIPN with or without evidence of neuropathic pain. Undoubtedly, the most important risk factor, consistently associated with greater CIPN, is the higher cumulative dose of chemotherapy [12]. Other reported risk factors include the history of uncontrolled diabetes, comorbid peripheral neuropathy, older age > 65 years, female gender, higher body mass index and low haemoglobin levels [12–15]. The impaired functional status, and longer duration of cancer have also been suggested to increase the risk of CIPN [16]. Nonetheless, other studies have found no such link between the majority of the latter risk factors and CIPN and it was suggested that methodological discrepancies and inadequately powered sample sizes may account for these conflicting results [17].

Tellingly, many of the potential predictors of CIPN have not been fully investigated to date in the context of chemotherapy-induced neuropathic pain (CINP). Considering that there is currently no evidence-based intervention to prevent CIPN or CINP [18], it remains clinically important to identify those patients most at risk for developing CINP to mitigate both the sensory symptoms and the neuropathic pain component of CIPN. Towards the latter view, further studies are warranted to explore the potential link between CINP and various unmodifiable and modifiable risk factors. Particularly, the likely association between gender or advanced age and the related risk of developing painful CIPN is modest, with limited availability of evidence-based data. Hence, this clinically important topic remains conflictingly addressed in the literature [19, 20].

Given the scarce literature in this area, the potential effect of gender and age on painful CIPN trajectories has yet to be determined. As such, to further ascertain the clinical phenotype of CIPN, according to unmodifiable risk factors related to demographic characteristics, the aim of the current study was to determine whether the incidence and severity of CINP vary, based on the patients' gender and age.

Patients and methods

Study design and participants

In accordance with the Declaration of Helsinki, we obtained approval from the Institutional Review Board of "Agios Andreas" Patras General Hospital, Greece before

conducting this retrospective, file-based study. An opt-out consent procedure was used owing to the retrospective, file-based nature of the study. The medical files of adult patients with various types of non-hematological malignancies that received any conventional chemotherapy were retrospectively reviewed. All these patients were referred over 4 years to document and quantify the presence of CIPN with or without CINP, for as part of the routine everyday practice clinical or for research purposes.

The inclusion and exclusion criteria are previously described in detail [11]. Briefly, patients, whose medical files included enough clinical information to serve the objectives purposes of the current study, had to be chemotherapy-naive with no evidence of peripheral nerve damage or neuropathic pain (postherpetic neuralgia, trigeminal neuralgia, spinal cord injury, etc.) of any other nature prior to the assessment or the onset of chemotherapy administration. Patients with comorbid systemic diseases, such as collagen or rheumatic disorders and renal insufficiency, etc., were excluded. Exception consisted the presence of comorbid well-controlled, uncomplicated diabetes mellitus and as such these patients were included for assessment.

From the medical files of enrolled patients, we then retrieved data concerning the demographic (biological gender, age) and clinical oncological characteristics (cancer and chemotherapy type as well as the cumulative chemotherapy dosage received). Moreover, clinical neurological data were thoroughly collected to document the incidence and further quantify the severity of CIPN as well as CINP.

The CIPN was clinically defined by the presence of a dose-related, symmetrical distal painful or painless paresthesia and dysesthesia for at least two subsequent chemotherapy courses without evidence of symptoms' remission [21]. The 7-item composite Total Neuropathy Score-clinical version (TNSc®) tool was employed to assess the incidence and severity of CIPN with the use of the following grading cut-offs: grade I (scores 1–7); grade II (scores 8–14); grade III (scores 15–21) while a score of > 21 was consistent with grade IV CIPN [22, 23].For this analysis, patients were classified to those with grade 0–1 (TNSc® score of 0–7) vs. grade 2–3 CIPN (TNSc® score of 8–21).

The CINP was defined as a pain generated from a disease or lesion of the somatosensory nervous system, clinically characterized by shooting or burning pain, hyperalgesia (continuous or paroxysmal abnormal hypersensitivity to stimuli) and allodynia, i.e., nociceptive responses to non-noxious stimuli [24]. The severity of CINP experienced by patients was clinically quantified and monitored, using the 11-point pain intensity numerical rating scale (PI-NRS), ranging from 0 to 10, where 0 represents "no pain" and 10 represents "worst possible pain" [25]. Once only, at the time of CINP first onset during chemotherapy, we also screened patients with the Douleur Neuropathique 4 (DN4) questionnaire, which is a tool, ranging from 0 to 10, with the ability to distinguish between nociceptive and neuropathic pain [26]. Patients were evaluated with TNSc® and PI-NRS at the time of CIPN and CINP onset during chemotherapy and monitored with the same tools at chemotherapy completion and 3 months afterward.

Finally, a propensity score matching analysis (PSMA) was conducted in the entire group of enrolled patients to create two equally gender-matched groups of subjects. To study the age effect on gender-matched patients, this variable was explored as continuous but also as categorized factor according to two age groups, i.e., those aged ≤ 65 years (group I) and patients aged ≥ 66 years (group II).

Statistical analysis

Descriptive data analysis presented categorical variables as observed counts and percentages, while continuous variables were described as either the mean with standard deviation or the median with range, depending on their distribution. Associations between dichotomous categorical variables were assessed using the chi-square test. For continuous data, parametric and non-parametric comparisons were conducted using the Student's t-test and Mann–Whitney U-test for two groups, and the Kruskal–Wallis test for multiple groups, as appropriate. To minimize confounding parameters when comparing the incidence of CINP into gender classes, propensity score matching with the nearest neighbor approach and using a caliper of 0.2*weighted standard deviation of the logit of the propensity score was applied. Matching criteria included uncomplicated diabetes, age and TNSc® score. The refined cohort resulting from this matching process was also used to identify factors associated with the likelihood of developing CIPN. A binary logistic regression analysis was conducted, employing a backward stepwise method to evaluate the following variables, gender, age, TNSc® score, and chemotherapy type. All tests were two-tailed and statistical significance was set at the $p < 0.05$ level. Statistical analysis was performed using SPSS for Windows (release 26.0; SPSS Inc., Chicago, IL).

Results

A total of 205 males (M) and 295 females (F) were initially included, and after PSMA, 191 patients of each gender were equally matched for age ($p = 0.97$), history of diabetes ($p = 0.89$), and overall TNSc scorings ($p = 0.94$); totaling 382 patients. Patients had a diagnosis of colorectal cancer (165; 43.2%; M/F: 90/75), lung cancer (101; 26.4%; M/F: 84/17), breast cancer (69; 18.1%; M/F: 0/69),

Table 1 Demographic and clinical characteristics of the original cohort and the results after the selection from propensity score matching analysis. Data on the incidence and severity of CIPN and CINP refer to those obtained at the end of chemotherapy for both the entire and PSMA cohorts

Entire cohort				***PSMA cohort***		
	Males *N* = 205 (%)	**Females *N* = 295 (%)**	***P* value**	**Males *N* = 191 (%)**	**Females *N* = 191 (%)**	***p* value**
Age	62.4 ± 8.5	58.8 ± 10.2	<0.001	62.1 ± 8.5	62.1 ± 8.7	0.97
Diabetes	32 (15.6)	40 (13.6)	0.52	31 (16.2)	29 (15.2)	0.89
TNSc (range)	8 (0–21)	8 (0–20)	0.84	8 (0–21)	8 (0–20)	0.94
CIPN	140 (68.3)	203 (68.8)	0.92	130 (68.1)	130 (68.1)	1
TNSc® (range)	10 (2–21)	10 (2–20)	0.55	10 (2–21)	10 (2–20)	0.9
CINP	55 (26.8)	72 (24.4)	0.60	52 (27.2)	53 (27.7)	1
PI-NRS (range)	7 (6–9)	7 (5–9)	0.025	7 (6–9)	7 (5–8)	0.09
PI-NRS≥7 (N; %)	24 (44.4)	19 (25.7)	0.037	22 (59.5)	15 (40.5)	0.1
TNSc® (range)	14 (4–21)	15 (8–20)	0.31	14 (5–21)	15 (8–20)	0.2

Abbreviations: *PSMA* Propensity Score Matching Analysis, *CIPN* Chemotherapy-Induced Peripheral Neurotoxicity, *TNSc®* Total Neuropathy Scale, clinical version, *CINP* Chemotherapy-Induced Neuropathic Pain, clinical version, *PI-NRS* 11-point pain intensity numerical rating scale

gynecological cancers (27; 7.1%; M/F: 0/27), head and neck cancer (13; 3.4%; M/F: 10/3) as also testicular cancer (7; 1.8%, M/F: 7/0) and received oxaliplatin (165; 43.2%; M/F: 90/75), paclitaxel (134; 35.1%; M/F: 45/89), cisplatin (52; 13.6%; M/F: 40/12) and a combination of paclitaxel and cisplatin (31; 8.1%; M/F: 16/15). The distribution relating to the incidence of cancer and chemotherapy types for the entire and PSMA cohorts is provided in supplementary table.

Gender effects on CINP incidence and severity

Overall, 130/191 males and 130/191 females experienced CIPN at the end of chemotherapy. As can be seen in Table 1, the incidence of CINP, occurring overall in 105 patients, was similar between males and females (52; 27.2% vs. 53; 27.7%; $p = 1$). The DN4 scorings at CINP onset were comparable between males and females (median 7, range 7–9 for both; $p = 0.9$). Similarly, the incidence and severity of CIPN were comparable between genders. The same applied for CINP. The severity of CINP at the end of chemotherapy, according to PI-NRS, showed a trend to significance between males and females (7 [range: 6–9] vs. 7 [range: 5–8], respectively; $p = 0.09$).

However, males demonstrated a trend to significance for higher rates of severe CINP (PI-NRS ≥ 7) at the end of chemotherapy [males: 59.5%, females: 40.5%; $p = 0.1$], despite having lower CIPN severities, according to TNSc® scoring than females (median 15 and range 10–18 vs. median 16 and range: 10–20; $p = 0.093$, respectively). Finally, at 3 months post-chemotherapy completion, the PI-NRS scorings were comparable (median 4.5 (range: 3–8) for males vs. 4 (range: 3–8) for females; $p = 0.56$).

Age effects on CINP incidence and severity

It was evident that 260 patients; 144 aged ≤ 65 years and 116 having ≥ 66 years, experienced comparable rates of CIPN of any severity, according to TNSc® sum scorings. Likewise, similar mean TNSc® values were disclosed between age groups (7.4 ± 6.2 for group I vs. 7.5 ± 6.1 for group II; $p = 0.931$).

Table 2 Comparison of the incidence and severity of CIPN and CINP between age groups, after completion of chemotherapy schedules

Variable	**Group I (≤ 65 years) *n*=216 N %**	**Group II (≥ 66 years) *n*=166 N %**	***p value***
Incidence of CIPN	144 66.6	116 69.9	0.51
Severity of CIPN, according to TNSc®			
Grade I (1–7 sum scoring)	25 11.6	29 17.5	0.37
Grade II (8–14 sum scoring)	70 32.4	55 33.1	
Grade III (15–21 sum scoring)	49 22.7	32 19.3	
Incidence of CINP	54 25.0	51 30.7	0.21
Severity of CINP, according to PI-NRS			
PI-NRS ≥ 7 (N; %)	28 45.9	22 50.0	0.41

Abbreviations: *CIPN* Chemotherapy-Induced Peripheral Neurotoxicity, *TNSc* Total Neuropathy Scale, clinical version, *CINP* Chemotherapy-Induced Neuropathic Pain, *PI-NRS* 11-point pain intensity numerical rating scale, *SD* Standard deviation

From a total of 105 patients experiencing CINP at completion of chemotherapy, 54 (25%) were aged ≤ 65 years and 51 (30.7%) were ≥ 66 years ($p = 0.214$). Patients being allocated in both age groups had comparable rates of CINP severities, according to the mean PI-NRS difference, with evidence of similar mean PI-NRS scorings between age groups (7.3 ± 0.7 for group I vs. 7.1 ± 0.8 for group II; $p = 0.584$). Likewise, both younger (28; 45.9%) and older (22; 50.0%) patients had comparable rates ($p = 0.412$) of severe CINP (PI-NRS ≥ 7). Table 2 describes the summary of differences related to the incidence and severity of both CIPN and CINP, according to age groups.

Factors associated with the likelihood of developing CINP

When the PSMA cohort was analyzed with logistic regression, it was evident that the likelihood to present CINP is independently associated with worse TNSc® scores (OR: 1.6; CI 95%: 1.42–1.78; $p < 0.001$) and was significantly lower for patients who received oxaliplatin, taxanes, or cisplatin alone compared to those who received a combination of taxanes and platinum drugs (reference group) [(oxaliplatin: OR: 0.11; CI 95%: 0.03–0.41; $p = 0.001$); (taxanes: OR: 0.089; CI 95%: 0.02–0.33; $p < 0.001$); (cisplatin: OR: 0.071; CI 95%: 0.016–0.31; $p = 0.001$)]. There was no evidence for any association between genders with increased incidence of CINP (OR: 0.8; CI 95%: 0.39–1.16; $p = 0.55$). However, it should be noted that a trend towards clinical significance was observed for an association between the presence of uncomplicated diabetes and increased incidence of CINP (OR: 2.13; CI 95%: 0.91-5; $p = 0.09$). Notably, patients with worst TNSc® severities (OR: 1.33; CI 95%: 1.03–1.72; $p = 0.028$) and older (≥ 66 years) males (combined variable age by sex) (OR: 1.08; CI 95%: 1.01–1.16; $p = 0.027$) presented a higher likelihood to experience severe pain (PI-NRS ≥ 7) at the end of chemotherapy.

Discussion

We have recently reported on a large sample size of 500 cancer patients that the presence of uncomplicated diabetes, the combination of paclitaxel plus cisplatin treatment and the increased severity of acute oxaliplatin neurotoxicity were mostly related to an increased risk of CINP development. There were no gender or age-related effects on the incidence and severity of CINP [11]. To further ascertain if indeed these two unmodifiable demographic factors can influence the clinical phenotype of CINP, we conducted PSMA to create equally balanced cohorts, according to gender. The PSMA approach provides the ability to reduce the effects of confounding factors in observational studies, so as to resemble some of the high-level qualitative characteristics of a randomized controlled trial [27].

With PSMA, we found, that overall, there were no significant gender and age differences in terms of incidence and severity of CINP. Nonetheless, we should note that males, compared to females, seem to present a higher proportion of worst pain raters (PI-NRS ≥ 7; 59.5% vs. 40.5%, respectively; $p = 0.1$); despite both genders presented a similar severity of CIPN, according to TNSc®.

When it comes to gender-related differences, there is limited evidence, from a pooled analysis of randomized clinical trials for gastrointestinal cancers treated with a platinum agent, to support the hypothesis that biological sex poses abilities to increase the risk of more frequent or more severe CIPN. In the latter publication, males were more liable than females for higher incidence of CIPN [27]; but not for more severe grade 3 or higher CIPN [28, 29]. On the contrary, the proportion of those reporting CINP was higher among females than males (49.0% ($n = 417/851$) vs. 24.3% ($n = 43/177$); $p < 0.001$) in 1029 cancer patients, included in a recently published French nationwide cross-sectional study [30]. Nonetheless, in line with our results, other previously published studies failed to identify an association between genders and painful CIPN [31]. Of note, bench-side evidence, might provide compelling mechanistic rationale for this lack of gender-related differences in CIPN, by demonstrating comparable expression of endocannabinoid system components in an experimental model of CINP [32].

With regards to age-related effects, it is evident from retrospective pooled analyses of cancer clinical trials, solely relying on clinician-reported outcome measures for CIPN severity, that cancer patients at a more advanced age are more prone to a moderate or severe CIPN [33, 34]. On the contrary, we have previously shown, that using both clinician- and patient-reported outcomes for assessing CIPN severities, that cancer patients with no major comorbidities who are aged over 65 years patients, are not more liable to CIPN following exposure to platinum compounds and taxanes [35, 36]. We further demonstrate herein, using PSMA, patient-reported (pain intensity) outcomes and objective evaluation (TNSc® items) for the assessment of CIPN severities, that age ≥ 66 years appeared to not have a direct increase of their risk for developing higher incidence and severity of CINP (painful CIPN). However, of note is our finding suggesting that older (≥ 66 years) male patients presented with a higher likelihood to experience severe pain (PI-NRS ≥ 7) at the end of chemotherapy.

Our findings are in agreement with a previously published study that prospectively aimed to determine if patient-reported and objective measures of CIPN differ by age among 425 cancer survivors, aged less than 65 years ($n = 260$) or ≥ 65 years ($n = 165$). This study concluded that despite having worse light touch, cold, and vibration sensations, older cancer survivors with CIPN reported less severe CINP and interference with activities of daily living, despite generally having worse severity of CIPN [37].

Our study has certain methodological limitations, mainly consisting of its retrospective, file-based design. Additionally, our study lacked neurophysiological and quality of life outcomes. Nonetheless, apart from the above-mentioned limitations, our study has significant strengths. Firstly, the qualitative outcome of the applied gender-matching process was excellent, because the PSMA cohort was nearly equally distributed amongst the two genders; with p values around 1, for significant variables, including age, history of uncomplicated diabetes, TNSc® scorings, and presence of either incidence

or severity of CIPN. Secondly, we characterized CIPN and CINP using both patient-reported and objective measures, including the use of the DN4 questionnaire at the first onset of CINP in order to be able to distinguish between neuropathic rather than nociceptive pain in cancer patients. This is, in our opinion, of paramount importance in any CINP setting, if we consider findings from a previously published French study evaluating the impact of chronic pain with or without a neuropathic component in cancer patients that revealed that chronic neuropathic pain (lasting > 6 months) was associated with higher pain intensity scores and had a greater impact on functioning or QoL than those with chronic pain without a neuropathic component [38].

To conclude, we were unable to identify significant gender and age-related differences in the incidence and severity of CINP, although males tend to present with a higher proportion of worst pain raters, while scoring lower in TNSc® severities. Nonetheless, even if our findings were not in keeping with gender and age-related differences in CINP trajectories, it is important to monitor not only the overall prevalence of CIPN, but also the prevalence of the different types of nociceptive or neuropathic pain experienced by cancer patients. Hence, further prospective longitudinal studies are needed to identify the true effects of different risk factors, including gender and age, for the development of more severe CINP in order to enhance decision-making towards improved management of painful CIPN routine in the daily clinical practice. Therefore, it is imperative to set up an internationally recognized consensus for the definition and management of different pain types in cancer patients that will greatly help clinicians understand the early signs of painful CIPN; thus, leading to early interventions, such as dose modifications of chemotherapy, referral to specialists and treatment with medications to alleviate the neuropathic pain component of CIPN.

Abbreviations

CINP	Chemotherapy-induced neuropathic pain (CINP)
CIPN	Chemotherapy-induced peripheral neurotoxicity
PSMA	Propensity Score Matching Analysis
PI-NRS	Pain intensity numerical rating scale
DN4	Douleur Neuropathique-4 questionnaire
TNSc®	Total Neuropathy Score-clinical
QoL	Quality of life
OR	Odds ratio
CI 95%	Confidence Interval95%
SD	Standard deviation

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
Conceptualization: JB, HK, and AAA; methodology: JB, and AAA; formal analysis: JB, and AAA; data curation: FK, JB, RV, HK and AAA; writing—original draft preparation: FK, JB, RV, PL, MA, DR, HK, AAA; writing—review and editing: FK, JB, RV, PL, MA, DR, HK, AAA; visualization: FK, JB, HK, AAA; supervision: JB, HK and AAA. All authors have read and agreed to the submitted version of the manuscript.

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

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of "Agios Andreas" Patras General Hospital. An opt-out consent procedure was permitted from the Institutional Review Board of "Agios Andreas" Patras General Hospital, owing to the retrospective, file-based nature of the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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