

Pancreaticoduodenectomy as a feasible choice for periampullary malignancy in octogenarians

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Abstract. The efficacy and safety of pancreaticoduodenectomy (PD) has not been yet studied in octogenarians in Greece. The present study reviewed records of all consecutive patients that underwent PD at the 4th Surgical Department of Attikon University Hospital (Athens, Greece) between January 1st, 2010 and December 31st, 2019. Differences between two age groups (group Y <80 years; group O >80 years) were analyzed. Study endpoints were length of stay, overall morbidity, 30-day mortality and overall survival (OS). There were 198 patients in Group Y (mean age, 65 years) and 20 patients in Group O (mean age, 82 years). Octogenarians had worse American Society of Anesthesiology score (>2; 31.3 vs. 65%; P=0.018). Median stay was not significantly different between the two groups (14 days vs. 16 days; P=0.307), neither was the 30-day mortality (6.1 vs. 5.0%; P>0.99). Median OS was similar between the two groups (35 months vs. 28 months; P=0.577). In a tertiary center in Greece, morbidity and mortality rates after PD were similar between the two groups. Patients should not be denied a PD, solely based on advanced age.

Introduction

Periampullary adenocarcinoma encompasses neoplasms arising from the epithelium of four distinct anatomic sites: ampullary adenocarcinoma, distal cholangiocarcinoma, duodenal adenocarcinoma, and pancreatic head adenocarcinoma (1). Pancreatic cancer is the most common periampullary adenocarcinoma and the fourth leading cause of cancer deaths in the United States (2). By the year 2030, it is estimated that 70% of all cancer cases and 85% of all cancer-related deaths are likely to occur in patients older than 65 years (3). Moreover, the older population in the European Union (EU) is rapidly growing. EU total population on January 1st 2018 was estimated at 512.4 million, 19.7% of which constitute people aged 65 or over. Interestingly, the subgroup of the very old (aged 85 years or more) is growing at a faster pace than any other age group. Between 2018 and 2050, the oldest population in the EU is estimated to more than double, up 130.3%. Across the EU member states, the highest share of persons aged 65 or older in the total population in 2018 was observed in Italy (22.6%) and Greece (21.8%), while the lowest share was observed in Ireland (13.8%) (4,5). It is well known that the incidence of solid tumor malignancy rises with age, becoming progressively much more common in the older brackets of the population.

As the percentage of patients in the older brackets increases, more patients seek surgical care as a chance to cure. Denying patients resection based on age alone seems unsustainable. In fact, designing a patient centered personalized treatment plan will require a better understanding of how these elderly patients perform after major pancreatic resections. Surgical resection and most specifically pancreaticoduodenectomy (PD) or Whipple procedure remains the standard of treatment for periampullary adenocarcinoma (6). Despite decades of improvement in surgical technique and postoperative care, this procedure still carries a high rate of post-operative morbidity and mortality (7,8). Systematic reviews about PD in elderly patients (older than 65 years) show controversial results regarding post-operative morbidity and mortality (9,10). Nonetheless, studies on patients older than 80 undergoing a PD report either a similar profile of morbidity

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Abbreviations: PD, pancreaticoduodenectomy; OS, overall survival; EU, European Union; AJCC, American Joint Committee on Cancer; ASA, American Society of Anesthesiology; CCI, Charlson Comorbidity Index; IPMN, Intraductal Papillary Mucinous Neoplasm; DGE, delayed gastric emptying

Key words: whipple, periampullary adenocarcinoma, pancreaticoduodenectomy, elderly patients, safe surgery, octogenarians, pancreatic cancer, Greece

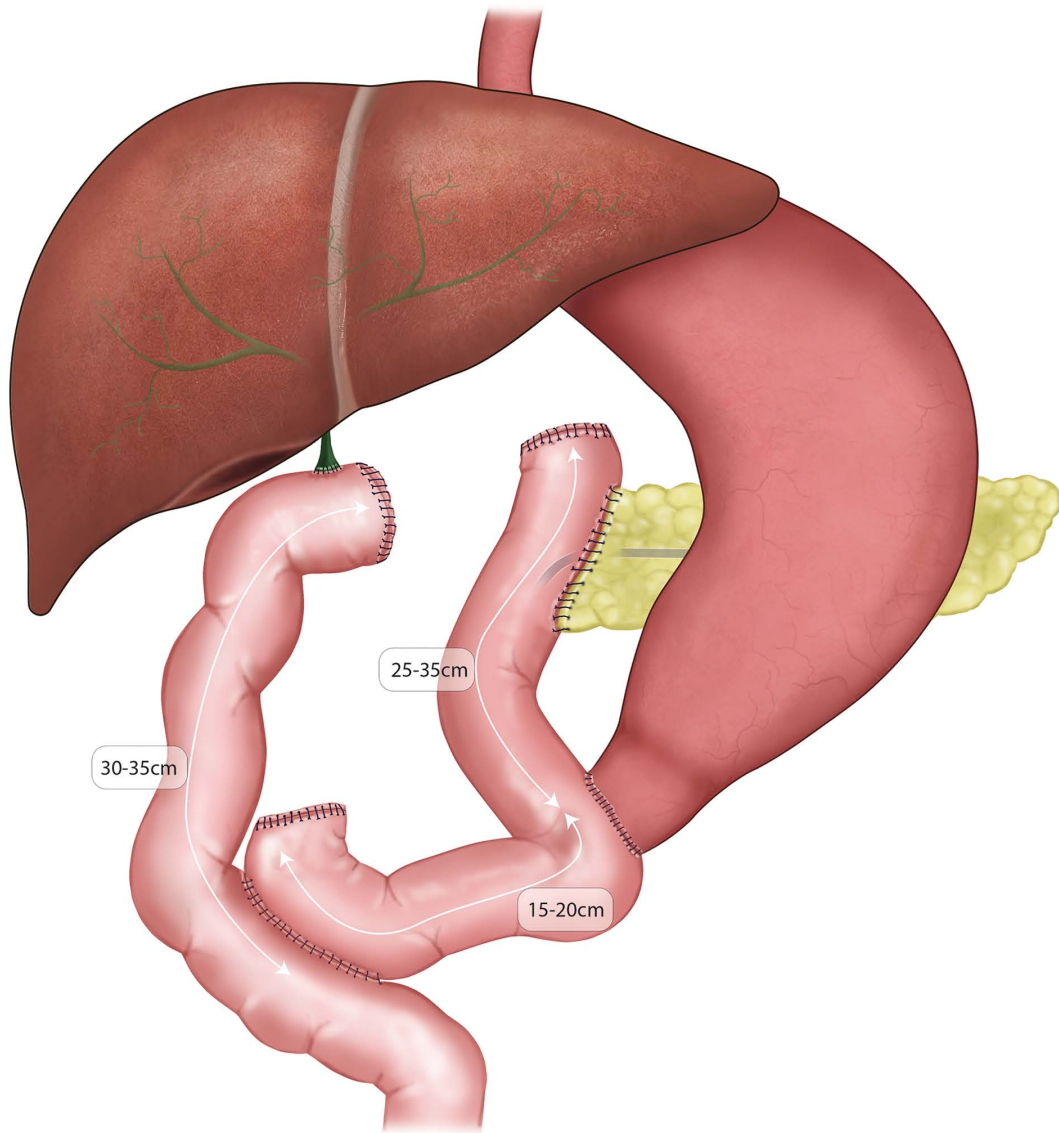


Figure 1. Pylorus preserving PD with Roux-en-Y configuration. This figure captures the anastomoses following PD of the technique used in 4th Department of Surgery, Attikon University Hospital, National and Kapodistrian University of Athens.

and mortality or a slight increase, albeit non prohibitive (11,12). In this context, in our tertiary referral center, we have observed a trend in performing PD more frequently on octogenarians during the last decade. To understand our unique population's characteristics, we opted to study the short-term outcomes and long-term survival after a PD for periampullary tumors in patients older than 80 years in our center and compare these to their younger counterparts.

Materials and methods

We retrospectively reviewed all consecutive patients who underwent a Whipple procedure from January 2010 until December 2019 at the largest tertiary, academic hospital in Greece (Attikon University Hospital). All the procedures were coordinated by Professor Vasileios Smyrniotis, while all involved surgeons were equally exposed to pancreatic surgery. Over the years, all periampullary cancer patients referred to our facility are evaluated by a multidisciplinary team; treatment is

then personalized according to stage and pathological features of the tumor as well as to patient's comorbidities. Typically, patients with resectable disease undergo surgical procedure; patients who are deemed borderline resectable receive neoadjuvant chemotherapy and are reevaluated for possible resection. Concerning older patients, the performance status score was useful; patients with a score 3 or 4 in ECOG scale may be discouraged of surgical treatment (13). Other than that, there were no specific selection or exclusion criteria.

Complete data from all patients were obtained from hospital charts and included patient demographics, comorbidities, medical history, tumor type, stage and histopathological features, perioperative events and complications, and status of disease at follow-up. Pathological staging of malignant tumors was performed according to the Tenth Edition of the Cancer Staging Manual edited by the American Joint Committee on Cancer (AJCC). Thirty-day mortality was defined as death within 30 days from operation. Overall survival was determined from date of operation until date of death from any cause.

Table I. Sample characteristics by age group (Y group age, 25-79; O group age, 80-89).

Variable	Y group (n=198)	O group (n=20)	P-value
Male sex, n (%)	110 (55.6)	7 (35.0)	0.100
Smoking status, n (%)			0.068
Smoker	82 (41.4)	5 (25.0)	
Non-smoker	79 (39.9)	13 (65.0)	
Ex-smoker	35 (17.7)	1 (5.0)	
N/A	2 (1.0)	1 (5.0)	
Hypertension, n (%)	98 (49.5)	16 (80.0)	0.007
Diabetes mellitus, n (%)	47 (23.7)	9 (45.0)	0.077
Coronary artery disease, n (%)	30 (15.2)	6 (30.0)	0.100
Dyslipidemia, n (%)	54 (27.3)	9 (45.0)	0.110
Personal history of solid malignancy, n (%)	20 (10.1)	1 (5.0)	0.590
Arrhythmias, n (%)	14 (7.1)	2 (10.0)	0.630
Pulmonary morbidity, n (%)	9 (4.5)	1 (5.0)	0.990
Hypothyroidism, n (%)	25 (12.6)	2 (10.0)	0.990
Hyperthyroidism, n (%)	3 (1.5)	0 (0.0)	0.990
Previous abdominal surgery, n (%)	96 (48.5)	12 (60.0)	0.337
ASA score, n (%)			0.018
I	20 (10.1)	0 (0.0)	
II	110 (55.6)	6 (30.0)	
III	60 (30.3)	13 (65.0)	
IV	2 (1.0)	0 (0.0)	
N/A	6 (3.0)	1 (5.0)	
Charlson Comorbidity Index (CCI), n (%)			<0.05
0	1 (0.5)	0 (0)	
1	1 (0.5)	0 (0)	
2	13 (6.6)	0 (0)	
3	32 (16.2)	0 (0)	
4	49 (24.7)	1 (5)	
5	59 (29.8)	1 (5)	
6	34 (17.2)	7 (35)	
7	7 (3.5)	7 (35)	
8	2 (1)	4 (20)	
Neoadjuvant therapy	4 (2.0)	0 (0.0)	
BMI, kg/m ² (IQR)	25.39 (23.38, 28.89)	25.15 (21.83, 27.46)	0.478

ASA, American Society of Anesthesiology; BMI, body mass index; IQR, interquartile range; N/A, Not Available.

Patients undergo epidural and general anesthesia before PD in our institution, unless it is contraindicated. Most patients were operated on with Pylorus Preserving PD and the restoration of the visceral continuity was achieved over a Roux-en-Y configuration: the short limb was used for pancreatico-jejunostomy and gastroenterostomy and the long limb for the hepatico-jejunostomy (Fig. 1). While the rest of the patients were operated on with the classical technique and the restoration was achieved through a single jejunal loop.

The patients identified were categorized into two groups, according to age at the time of surgery: Group Y (<80-year-old) and Group O (≥80-year-old). Variables analyzed in the two groups included demographics, intra- and post-operative outcomes. Sample characteristics were summarized through

absolute (N) and relative (%) frequencies (categorical variables) or median and interquartile range-IQR (continuous variables). Summary statistics were given by age group (<80 or 80+ years) and overall. P-values in the respective tables were based on Fisher's exact test for categorical variables and non-parametric Mann-Whitney U-test for continuous variables. Analysis of the overall mortality was based on survival methods. More specifically, survival probabilities over time by group were estimated and graphically presented using the Kaplan-Meier method whereas for the respective between groups comparison the log-rank test was used. All statistics performed were two-sided and declared at the 5% significance level. The key study endpoints were length of stay, overall morbidity, perioperative mortality and median survival. There were no experiments

Table II. Intra-operative outcomes by age group (Y group age, 25-79; O group age, 80-89).

Variable	Y group (n=198)	O group (n=20)	P-value
Operation duration, min (IQR)	228 (185, 325)	255 (180.0, 342.5)	0.745
RBC, n (%)	0 (0, 2)	1 (1, 2)	0.084
FFP, n (%)	0 (0, 2)	0 (0, 0)	0.406
Epidural anesthesia and analgesia, n (%)	132 (66.7)	12 (60.0)	0.799
Vein reconstruction, n (%)	2 (1.0)	0 (0.0)	>0.999

RBC, red blood cells; FFP, fresh frozen plasma; IQR, interquartile range.

Table III. Pathology findings, by age group (Y group age, 25-79; O group age, 80-89).

Variable	Y group (n=198)	O group (n=20)	P-value
Histological type (grouped), n (%)			0.452
IPMN	12 (6.1)	1 (5.0)	
Pancreatic NET	7 (3.5)	0 (0.0)	
Adenocarcinoma			
Pancreas	121 (61.1)	13 (65)	
Ampullary	25 (12.6)	2 (10)	
Distal bile duct	21 (10.6)	1 (5)	
Duodenal	4 (2)	1 (5)	
Other	8 (4.1)	2 (10)	
Stage, n (%)			0.008
I/IA	9 (4.5)	1 (5.0)	
IB	25 (12.6)	9 (45.0)	
II/IIA	30 (15.2)	1 (5.0)	
IIB	67 (33.8)	4 (20.0)	
III/IIIA/IIB	49 (24.7)	2 (10.0)	
Unclassified	18 (9.1)	3 (15.0)	

IPMN, intraductal papillary mucinous neoplasm; NET, neuroendocrine tumor.

performed for the purposes of this study. All methods were carried out in accordance with relevant guidelines and regulations. The study received ethical approval and was conducted with permission of the Institutional Review Board and Ethics Committee of Attikon University Hospital (47929/16.12.16).

Results

Between 2010 and 2019, 218 patients underwent a Whipple procedure at the department of surgery at Attikon University Hospital. Of these, 20 (9.1%) were 80 years or older. The study population included 117 men and 101 women with a median age of 67 years (range 25-88) at the time of surgery. The median age of the Y group was 66 (range 25-79) and of the O group was 81.5 (range 80-88). Table I describes the demographics and comorbidities of the two study groups as well as whether they received neoadjuvant therapy or not. There were no differences in terms of gender composition (male 55.6 vs. 35.0%, $P=0.100$) or Body Mass Index (BMI) status ($P=0.478$). American Society of Anesthesiology (ASA) scores were worse in the octogenarian group (ASA 3-4: 31.3 vs. 65%,

$P=0.018$), as were the Charlson Comorbidity Index (CCI) scores (CCI >6 : 21.7 vs. 90%, $P<0.05$). However, there were no major differences in the incidence of patients' comorbidities, except for hypertension (49.5 vs. 80%, $P=0.007$).

Intra-operative outcomes. Table II describes intra-operative outcomes and hospitalization days for the two study groups. No differences were noted in terms of operative time, rate of portal vein resection and reconstruction, type of anesthesia or analgesia and number of units of blood transfused.

Pathology. Most neoplasms were adenocarcinoma of the pancreas in both groups (61.1 vs. 65%) followed by ampullary adenocarcinoma (12.4%), distal cholangiocarcinoma (10.1%) and Intraductal Papillary Mucinous Neoplasm (IPMN) (6%). Most cancers were stage II and III in group Y, while stage I and II in group O (Table III).

Post-operative outcomes. Overall morbidity (Clavien-Dindo ≥ 3) was equally distributed between the two groups (26.8 vs. 25%, $P=0.895$). No differences were noted in terms

Table IV. Post-operative outcomes, by age group (Y group age, 25-79; O group age, 80-89).

Variable	Y group (n=198)	O group (n=20)	P-value
Pancreatic fistula, n (%)			0.399
No fistula	148 (74.7)	16 (80.0)	
A	20 (10.1)	1 (5.0)	
B	15 (7.6)	3 (15.0)	
C	15 (7.6)	0 (0.0)	
Post-operative hemorrhage, n (%)	22 (11.1)	1 (5.0)	0.703
Delayed gastric emptying, n (%)	44 (22.2)	5 (25.0)	0.781
Re-exploration, (%)	22 (11.1)	1 (5.0)	0.703
Morbidity, n (%)			
Clavien-Dindo Grade I	26 (13.1)	4 (20.0)	
Clavien-Dindo Grade II	33 (16.7)	4 (20.0)	
Clavien-Dindo Grade IIIa	18 (9.1)	2 (10.0)	
Clavien-Dindo Grade IIIb	4 (2.0)	0 (0.0)	
Clavien-Dindo Grade Iva	13 (6.6)	2 (10.0)	
Clavien-Dindo Grade IVb	0 (0.0)	0 (0.0)	
Clavien-Dindo Grade V	18 (9.1)	1 (5.0)	
Post-operative need for ICU care, n (%)	25 (12.6)	3 (15.0)	0.728
30-day mortality, n (%)	12 (6.1)	1 (5.0)	0.990
Length of stay, days (IQR)	14 (10, 22)	16 (10.5, 23.0)	0.307
Median survival time, months (IQR)	35 (26, 42)	28 (6, non-estimable)	0.577

ICU, intensive care unit; IQR, interquartile range.

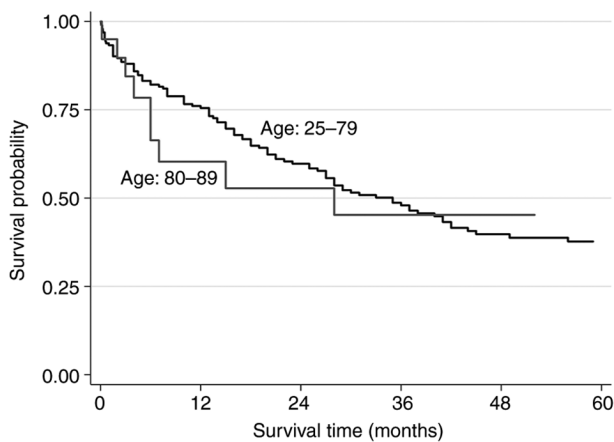


Figure 2. Kaplan-Meier survival estimates by age (<80/≥80).

of pancreatic fistula, hemorrhage, delayed gastric emptying (DGE) or reoperation rates. Length of hospitalization was not significantly different between younger and older patients (14 days vs. 16 days, $P=0.307$), neither was the 30-day mortality [12 patients (6.1%) vs. 1 patient (5%), $P>0.99$]. Follow-up was available for 214 patients (98.2% of our population). Mean follow-up time was 30.6 months for Group Y and 16.3 months for Group O. The 1-, 2- and 5-year survival rate was 75.5, 59.7 and 37.7% for Group Y and 60.3, 52.8 and 45.2% for Group O respectively (Fig. 2). Median overall survival (OS) was 35 months for patients younger than 80 years and 28 months for the octogenarians (log-rank test $P=0.577$) (Table IV).

Discussion

PD is a complex procedure, associated with high rates of morbidity. However, it remains the standard treatment for patients with periampullary neoplasms and especially for head pancreatic adenocarcinoma (7). Advanced age seems to be a risk factor regarding pancreatic cancer (2).

As the segment of the Greek population over age 80 has grown in the last several years, similar to other EU member states, in our tertiary referral center we have seen the portion of octogenarians presenting with a periampullary malignancy and receiving a PD increase as well. This study shows that patients over the age of 80 can safely undergo a PD. These patients can expect a profile of perioperative morbidity and mortality that does not differ from their younger counterparts'. In fact, we have found that octogenarians cared for in our center can expect a fair oncologic outcome with an overall median survival higher than two years after successfully undergoing their operation, without the implementation of specific steps to reduce morbidity and mortality. A bigger portion of the octogenarians were operated on, in a more favorable stage (45%-Stage IB) than the younger patients. That may be explained because by the slower progress of cancer in elderly and the frequent imaging studies of older patients due to other comorbidities.

Previous studies have analyzed the outcomes of PD in patients older than 80 years. Among them, studies have reported that octogenarians are more prone to morbidity, and when serious morbidity occurs, they are more prone to mortality (14-22). Conclusively, octogenarians can safely

undergo a complex gastrointestinal operation, albeit being more fragile, they seem to tolerate complications with less resilience than their younger counterparts. In our study, even if octogenarians had more postoperative complications than younger patients, there was no significant difference in 30-day mortality and OS. This is probably due to the small sample and it is not representative.

Regardless, authors appear to agree that PD is a safe option for elderly patients as long as there is careful selection depending on their preoperative workup (14-21). In these series, age appears to be less important than physiologic ability. Adding to that, some authors have proposed specific criteria for elderly patients which quantifies this physiologic ability, by assessment of cardiac and pulmonary function, nutritional status, daily activity status as well as psychological and independence status (21). Although specific scores were not used regularly during the past time period, the multidisciplinary team after the results of this study selects patients to receive surgical treatment, with careful consideration of Frailty index, Performance status score and CCI. Frailty index could be a reliable tool to assess the physiologic ability of older patients.

Performing a pancreatectomy in octogenarians with pancreatic cancer has been challenged recently: a 2015 multi-institutional study from Japan which compared a group of octogenarians who were operated for pancreatic malignancy with a group of elderly patients who were treated only with chemotherapy and possibly radiation showed no superiority of surgery in comparison to chemo and radiotherapy, although the patients who completed both resection and adjuvant chemotherapy had the best overall survival (23). The same group has also published in 2016 their experience in pancreatic resection comparing their octogenarians vs. their younger patients and found that the prognosis of octogenarians was poorer than that of younger patients for both resectable and borderline resectable tumors; importantly, there were few long-term survivors in their elderly group, especially among those with borderline resectable pancreatic cancer (24). These results clearly showcase the importance of careful patient selection especially in the extreme of age, and it also underscores the importance of referring these patients to a tertiary level center of excellence.

This study has several potential limitations. The main limitation is the retrospective nature of our review. We employed methodological strategies to minimize the difficulties in accurately gathering the retrospective morbidity data. First, complications such as pneumonia, urinary tract infection or wound infection (all regarded as Clavien-Dindo classifications <3) that could have been under documented in our patients' medical records charting system over the years were excluded. We were also not able to record some preoperative parameters such as biliary stenting, bilirubin levels, presence of cholangitis, hemoglobin levels, serum albumin levels. On the other hand, overall morbidity was accurately captured, for our discharge summary specifies whether the post-operative course of each patient was uneventful or not. Secondly, since the date of the operation and date of discharge from the hospital are always delineated in the electronic medical record, the hospitalization days were used as an additional quality measure of assessing for under reported postoperative morbidity. Our results show similar length of stay for elderly

patients (14 days vs. 16 days), which supports the fact that there was no significant difference in patients' morbidity. We showed herein that our octogenarians had a worse overall ASA score than our younger patients. Patients that either received adjuvant chemotherapy or were not operated or denied surgical treatment, even being fully informed, were not recorded. It would be interesting to compare the results of this study with the aforementioned group of patients. Lastly it is worth to mention that we have added a small number of patients in both our groups who had IPMN, a premalignant entity, as well as some adenomas which tips the scales to a better median survival for both groups. The grade of IPMN was not recorded in our study.

It is important to highlight that the population will continue to grow older, and as such more patients in the extreme of age will present with periampullary pathology and malignancy. We have shown in our study that undergoing a PD is safe and renders a significant survival benefit in octogenarians. Patients should not be denied a curative surgical option for periampullary disease, solely based on advanced age. Future studies, using larger and prospective databases, should include preoperative parameters and specific selection criteria, as careful and detailed preoperative assessment is deemed crucial to choose PD as a safe therapeutic option in octogenarians.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SP, TS, PK and VN acquired the data and drafted the first edition of manuscript. NP was responsible for the statistical analysis and, together with PV, PM and IM, interpreted the data and critically revised the manuscript. NA, VS and IH conceived and designed the study, revised the draft and formed the final edition of the manuscript. SP, VN and TS confirm the authenticity of all the raw data. All authors approve the final edition of the manuscript.

Ethics approval and consent to participate

This retrospective study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval was waived by the local Ethics Committee of Attikon University Hospital in view of the retrospective nature of the study and all the procedures being performed were part of the routine care. The study protocol including patients' consent was approved by Institutional

Review Board and Ethics Committee of Attikon University Hospital (approval no. 47929/16.12.16).

Patient consent for publication

Written informed consent regarding publishing data was obtained from all individual participants included in the study.

Competing interests

The authors declare that they have no competing interests.

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