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# Increasing pancreatic cancer is not paralleled by pancreaticoduodenectomy volumes in Brazil: A time trend analysis

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ABSTRACT

*Background:* Currently, surgical resection represents the only curative treatment for pancreatic cancer (PC), however, the majority of tumors are no longer resectable by the time of diagnosis. The aim of this study was to describe time trends and distribution of pancreaticoduodenectomies (PDs) performed for treating PC in Brazil in recent years.

*Methods:* Data were retrospectively obtained from Brazilian Health Public System (namely DATASUS) regarding hospitalizations for PC and PD in Brazil from January 2008 to December 2015. PC and PD rates and their mortalities were estimated from DATASUS hospitalizations and analyzed for age, gender and demographic characteristics.

*Results:* A total of 2364 PDs were retrieved. Albeit PC incidence more than doubled, the number of PDs increased only 37%. Most PDs were performed in men (52.2%) and patients between 50 and 69 years old (59.5%). Patients not surgically treated and those 70 years or older had the highest in-hospital mortality rates. The most developed regions (Southeast and South) as well as large metropolitan integrated municipalities registered 76.2% and 54.8% of the procedures, respectively. LMIM PD mortality fluctuated, ranging from 13.6% in 2008 to 11.8% in 2015.

*Conclusions:* This study suggests a trend towards regionalization and volume-outcome relationships for PD due to PC, as large metropolitan integrated municipalities registered most of the PDs and more stable mortality rates. The substantial differences between PD and PC increasing rates reveals a limiting step on the health system resoluteness. Reduction in the number of hospital beds and late access to hospitalization, despite improvement in diagnostic methods, could at least in part explain these findings.



## Introduction

Pancreatic cancer (PC) is the 4th leading cause of death worldwide [1]. In Brazil, PC is the 13th most prevalent cancer in men and the 10th most prevalent in women [2]. PC incidence and mortality rates are increasing in most parts of the world, being higher in high-income areas, intermediate in South and Central America and Eastern Asia, and lower in low-income areas [3–5]. Although there has been an overall reduction in tobacco-related neoplasms in Europe and North America, PC mortality trends for the next years and decades is not favorable [6–9].

The only potentially curative therapy for PC is complete surgical resection but, at the time of diagnosis, 80%–90% of the tumors are no longer resectable [10,11]. Most PCs involve the pancreatic head, location that determines whether the patient will undergo a pancreaticoduodenectomy (PD), the Whipple procedure. PD is an abdominal operation with a significant risk of postoperative morbidity and mortality [12,13]. Risk factors for pancreatic surgery are related to the pancreatic characteristics, age of the patients, comorbidities, and also to the procedure itself [13]. On the other hand, due to consistent progress in surgical procedures, operative rates for pancreatic tumors have increased significantly, being offered even to older patients with additional comorbidities [14,15]. Recent data suggest that a certain critical caseload volume is

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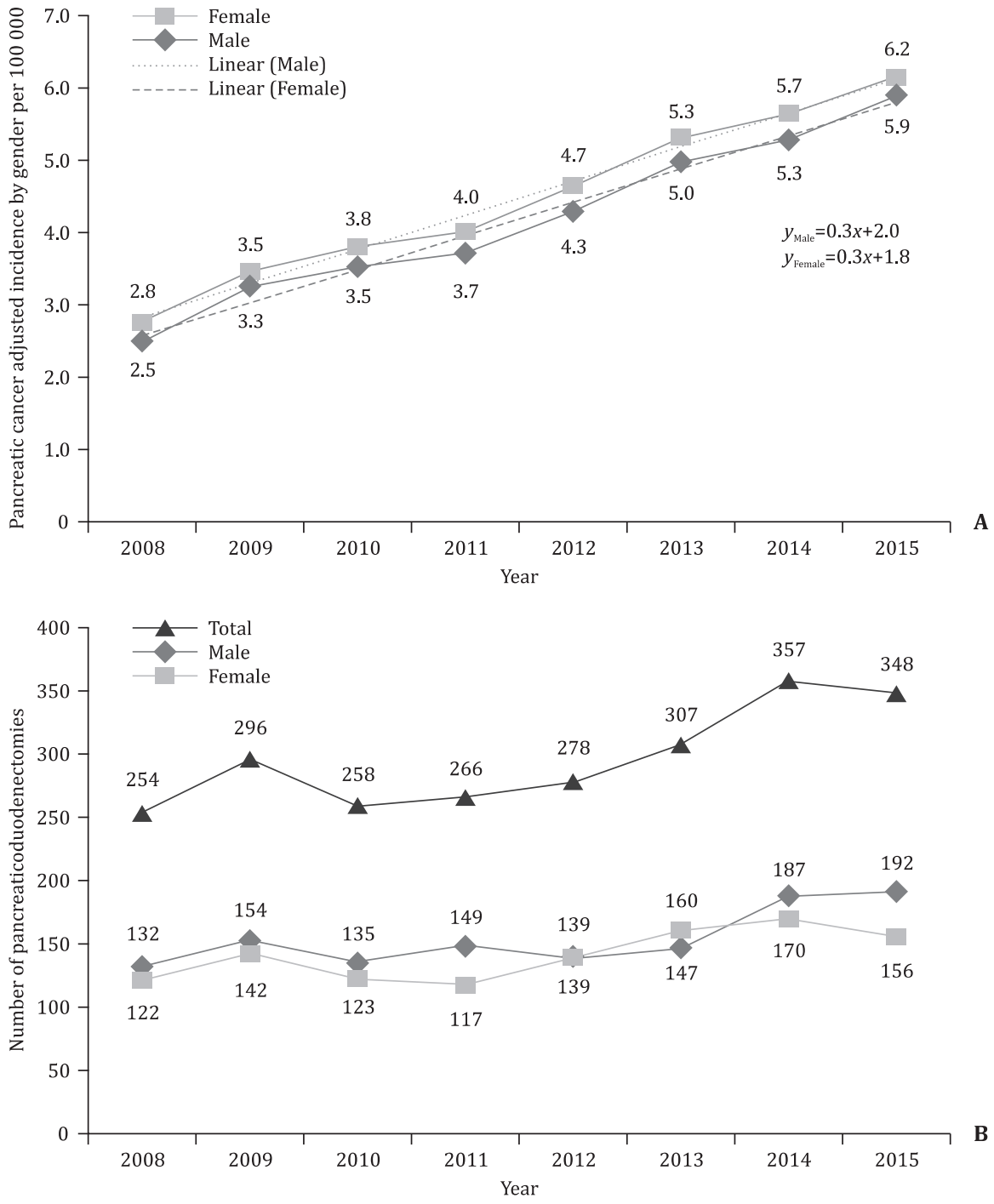


**Fig. 1.** Pancreatic cancer incidence (**A**) and the number of pancreaticoduodenectomies (**B**), by gender, estimated from hospitalizations in Brazil from 2008 to 2015.

required to undertake this kind of surgery with low mortality, because the results probably are influenced by case volume per surgeon and institution [16,17]. Major centers in Western countries report remarkably low rates of perioperative mortality, of less than 5% [18,19]. Nevertheless, there are considerable variations among centers worldwide. Hence, the value of regionalization and centralization of PD procedures has been under debate [20,21].

In Brazil, a recent study observed that PC incidence rates increased 87% from 2005 to 2012. Such increase in PC rates was mainly driven by people over 50 years old [22]. However, population-based data on cancer treatment are still limited in the country. Therefore, the aim of this study was to analyze rates, age-related in-hospital mortality and time trends of PD for PC in Brazil. In particular, demographic and geographic aspects related to urbanization and conurbation were taken into account, in order to evaluate possible patterns of regionalization and their potential influence in outcomes.

## Methods

### *Data source*

Data from the Health Informatics Department of the Brazilian Ministry of Health (DATASUS) (http://www2.datasus.gov.br/DATASUS) were searched. DATASUS registries include hospital admission and discharge information, medical procedures and

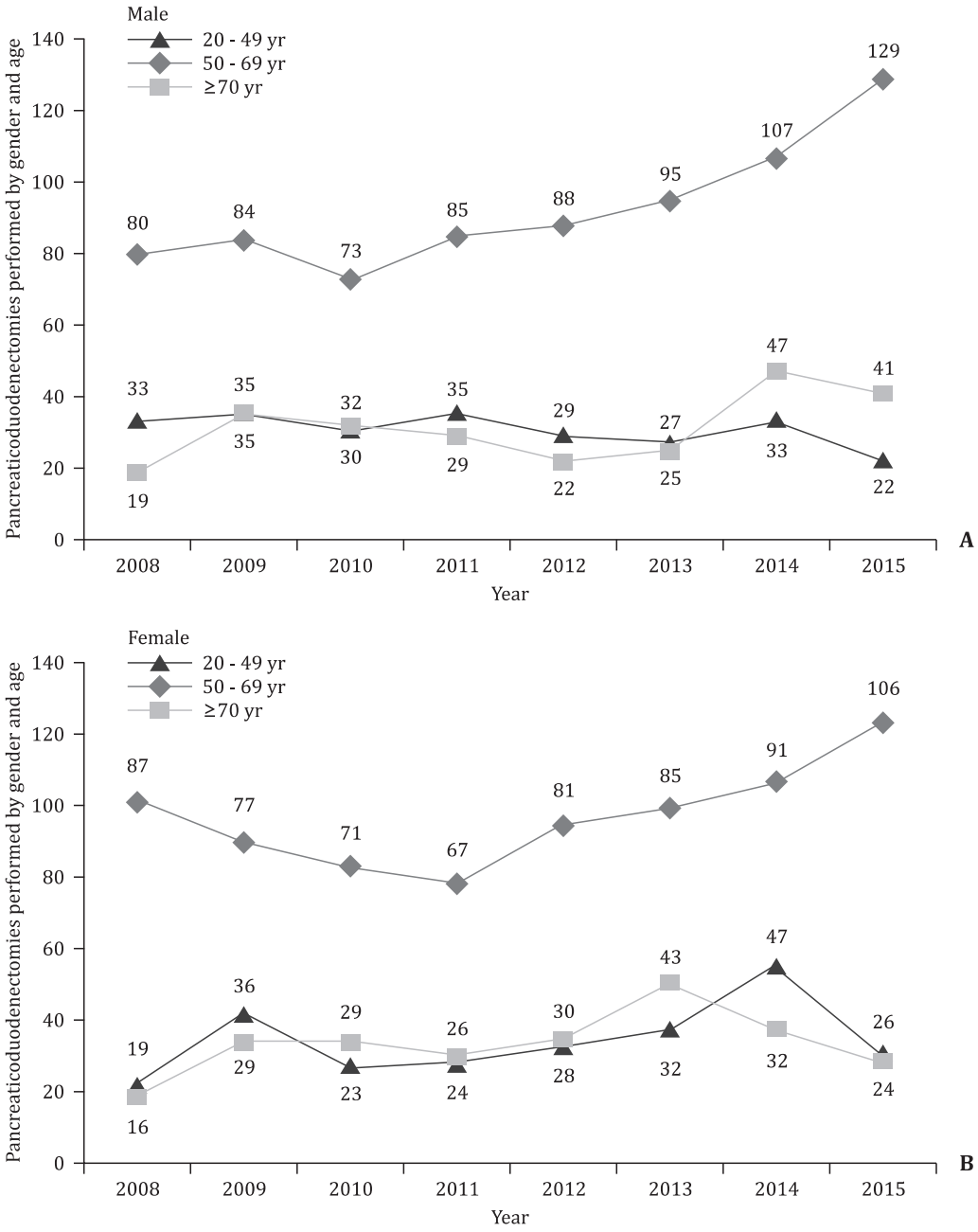


**Fig. 2.** Number of pancreaticoduodenectomies performed for pancreatic cancer by gender and age, estimated from pancreatic hospitalizations in Brazil from 2008 to 2015, males (**A**) and females (**B**).

mortality, reference tables and demographic data (age, gender, municipality) collected by the Instituto Brasileiro de Geografia e Estatística (IBGE; Brazilian Institute of Geography and Statistics). Patients under 20 years old were excluded. PC incidence and PD for PC rates were estimated from hospital discharge medical records and adjusted to available hospital beds. DATASUS covers approximately the entire Brazilian population, so we assumed hospital-based registries for PC and PD would consistently reflect actual disease and surgical procedure numbers.

*Study design, population and variables*

Registries obtained from DATASUS from January 2008 to December 2015 were searched for hospitalization records of patients with an *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* code of PC (*ICD-10* code: 25.0–25.9), 20 years or older, who underwent PD. The period of study was selected based on the most recent and consistent data available. Relevant data included gender, age and information of the town (municipality) of residence at the time of hospital admission and death. Age and gender-standardized rates concerning incidence, PD procedures and mortality (estimated from hospitalization records) were computed. Age groups were stratified as 20–49 years, 50–69 years and 70 years or older [22].

Geographic distribution was the result of individual analysis of PC hospitalization rates per 100 000 inhabitants in each municipality. Data collected from DATASUS included hospitalizations from all 5565 Brazilian municipalities distributed in 27 federative units and gathered in 5 geographic macroregions (north, northeast, southeast, south and central west). PD data were analyzed with respect

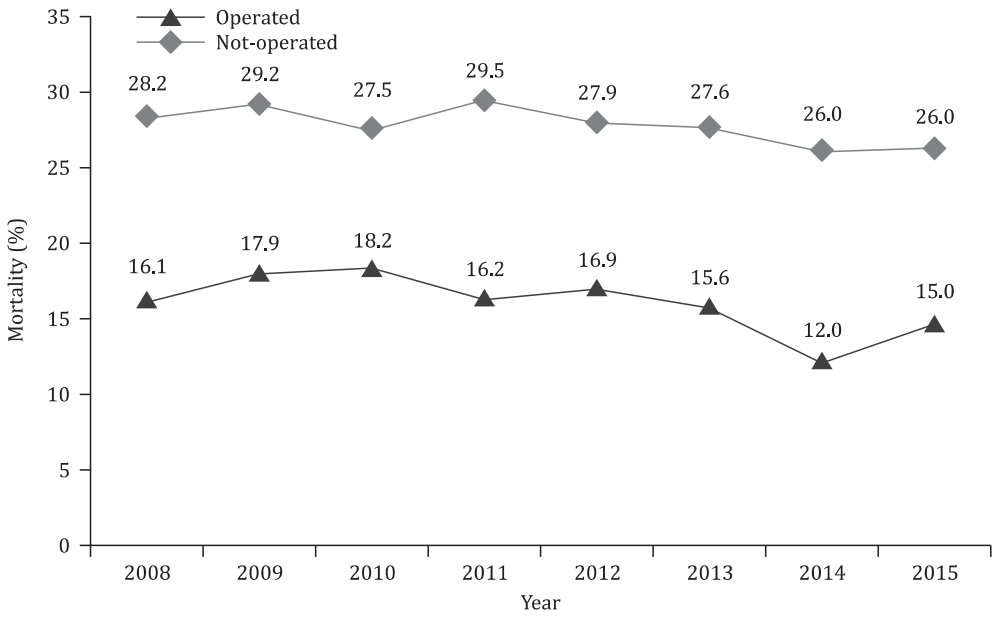


**Fig. 3.** Pancreaticoduodenectomy mortality rates (%) estimated from in-hospital deaths in Brazil from 2008 to 2015.

not only to geographic distribution, but also to take into account the municipality size where they were performed and its relation to metropolitan regions. A model that classifies municipalities considering the population and demographic density was used in this study. According to this model, municipalities are classified as rural small-sized (<50 000 inhabitants or <80 inhabitants/km$^2$), rural medium-sized (≥50 000 inhabitants or ≥80 inhabitants/km$^2$, even if population is <50 000 inhabitants) and true urban centers (>100 000 inhabitants) [23].

*Statistical analysis*

PC hospitalization rates were adjusted to the totality of available hospital beds in Brazil, 2015. Estimates of resident population were obtained from IBGE projections for 2015. Linear regression was applied to evaluate temporal trends in PC incidence by gender using Microsoft Excel Software (Microsoft Excel for Mac 2011, Version 14.4.9, 2010; Microsoft Corp, Redmond, Wash) and statistical analysis was performed using statistical software package SPSS for Windows (Version 20, SPSS Inc., Chicago, IL, United States). Exploratory procedures were applied to the data, and summary descriptive statistics and graphical displays were generated by Tabwin 3.2 either for all cases or separately for groups of cases.

## Results

*Hospitalizations for pancreatic cancer*

The age-standardized incidence for PC in Brazil, estimated from hospitalizations, increased 121.4% in men (from 2.8 to 6.2 per 100 000 inhabitants) and 136% in women (from 2.5 to 5.9 per 100 000 inhabitants) in the study period. Incidence by gender were higher in men (52.2%) than in women (47.8%) and the male/female incidence ratio was 1.05:1 (Fig. 1A).

*Pancreatoduodenectomy numbers, mortality, and their trends*

From 2008–2015, an estimated 2364 PDs were performed for PC in Brazil in people 20 years or older. The number of procedures performed annually increased 37% in the period, from 254 PDs in 2008, a peak of 357 in 2014 and 348 PDs in 2015 (Fig. 1B). Operative rates were higher in males (52.2%) than in females (47.8%). The estimated relative frequency of PDs for PC decreased from 7% in 2008 to 4% in 2015. Analysis of operative rates by age showed similar results in males and females. Patients aged 50–69 years underwent 59.5% of PDs. Operative rates for those aged 70 years or older were similar to those aged 20–49 years (20.3% and 20.3%, respectively) (Fig. 2).

In-hospital mortality rates of patients who underwent PD ranged from 12.0% (2014) to 18.2% (2010), lower than mortality rates of patients not operated (26.0% in 2014 to 29.5% in 2011) (Fig. 3). Mortality in the elderly (70 years or older) who underwent PD was lower (32.7% to 19.0%) than mortality observed in the same age group not submitted to PD (35.9% to 33.4%).

PD mortality rates were higher for patients 70 years or older (12% to 41% in males and 14% to 38% in females), and ranged from 10% to 23% and 12% to 20% for those aged 50 to 69 years (males and females, respectively). The lowest PD mortality rates were observed in those aged 20 to 49 years (3% to 12% and 0 to 14%, in males and females, respectively) (Fig. 4).

*Nationwide distribution of pancreaticoduodenectomy procedures*

Throughout the study period, the majority of PDs were performed in the southeast (52.7%) and south (23.4%) macroregions, the most industrialized and developed in Brazil, that together comprised 76.2% of the PDs. The number of PDs in the southeast was 12 times higher than that in the north region, where only 4.4% of PDs were performed. Nevertheless, the northeast region showed the highest increase in the number of PD performed in the period (75%), the southeast and south regions having registered increases of 40.5% and 15.3% respectively (Fig. 5).

PD rates were remarkably higher in large-sized metropolitan integrated municipalities (LMIM) (54.8% of the procedures), and the lowest rates were registered in small-sized metropolitan integrated municipalities (SMIM) (1.3% of the procedures). Overall, LMIM displayed the more stable mortality rates and frequently, lower rates compared to the ones observed in the large-sized municipalities not integrated to metropolitan regions (LMNIM), and also the medium sized municipalities integrated (MMIM) or not-integrated to metropolitan regions (MMNIM) (Table 1).

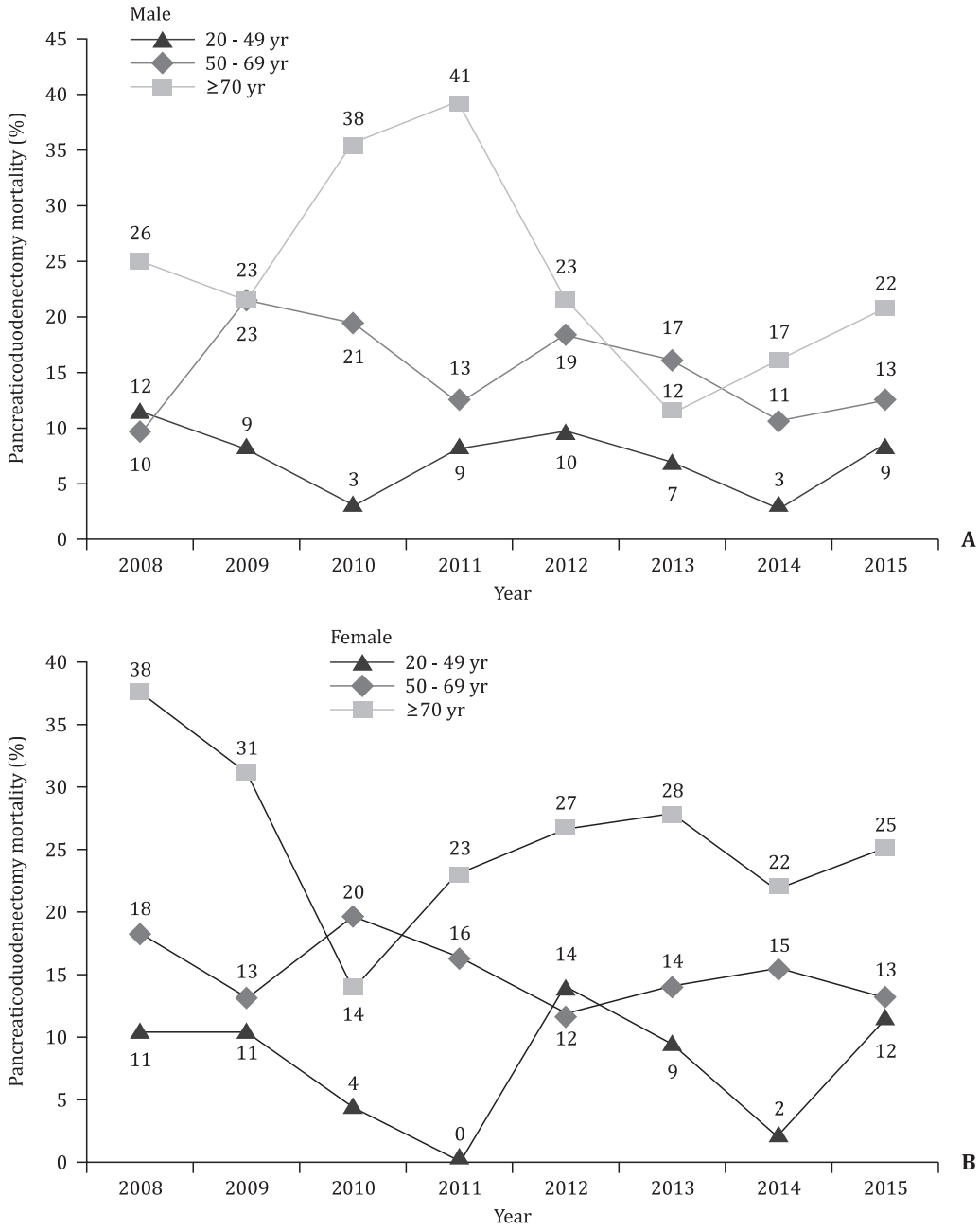


**Fig. 4.** Pancreaticoduodenectomy mortality rates (%) by gender and age estimated from in-hospital deaths in Brazil from 2008 to 2015, males (**A**) and females (**B**).

## Discussion

In this study, we describe for the first time to our knowledge, data on the PD surgical treatment for PC in Brazil over a recent period of time (2008 to 2015).

PD, with the possible addition of neoadjuvant or adjuvant therapy, is the current standard of care for adenocarcinoma originating in the pancreatic head, neck and uncinate process [24,25]. Although PD was developed in the early thirties, it became more frequent only after the 1980s, when highly complex surgical digestive centers developed, reducing the previous high mortality rates associated with PD. Ever since, institutions performing large volumes of PDs have been reporting progressively better results and, nowadays, high volume centers perform PD with a mortality rate of less than 5% [26,27]. Some reasons for increasing safety of pancreatic resections have been attributed to improved methods for patient staging and selection, advances in operative technique and perioperative management and consolidation of procedures to higher volume centers [28–30].

Our analysis of the records obtained from the Health Informatics Department of the Brazilian Ministry of Health (DATASUS) indicated a substantial increase of hospital admissions for PC during the study period, not paralleled by the number of PDs. Nevertheless, in-hospital mortality rates of patients undergoing PD were remarkably lower than the rates of patients who were not operated for PC and a decreasing mortality trend was noticed for operated patients as well. Most PDs were performed in large-sized metropolitan integrated municipalities, which also presented the lowest mortality rates in the country.

The increasing of PC in Brazil observed in a recent study of our group [22] is in accordance with international trends for PC [1], and is likely to reflect the relatively recent and progressive

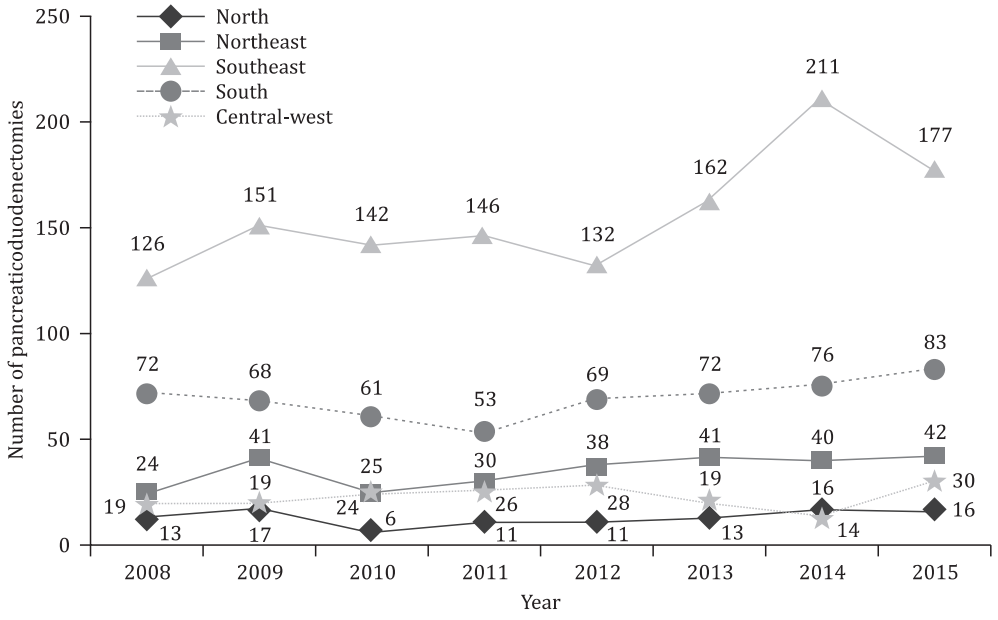


**Fig. 5.** Distribution of pancreaticoduodenectomies performed by macroregions in Brazil from 2008 to 2015.

aging of the population [31]. Nevertheless, it is also possible that earlier access to healthcare units, improvement of diagnostic methods and notification quality, developed in the last decade, may have influenced the recent increasing rates of PC observed in the country. In addition, PC was characterized as an urban disease, with higher rates localized in the more developed macroregions of the country (southeast and south), the state capital cities (mainly those with the highest Human Development Index-HDI) and large-sized metropolitan integrated municipalities [22]. In this sense, the demographic rates and trends of PD in Brazil analyzed in the present study are consistent with the distribution of PC previously described: operative rates are much higher in the southeast and the south, as well as in large-sized metropolitan integrated municipalities, where high complexity centers predominate [31]. As expected, PD was remarkably less performed in small-sized metropolitan integrated municipalities. This fact may be related to the current urban dynamics phenomenon that affects contemporary cities, such as the increased availability of transportation systems allowing the mobility of people to central cities in order to use their services, including the health care units [32].

In contrast to results of a study from another developing country showing increased rates of PDs for PC [33], in this study we did not find a corresponding increase in PDs. Whereas PC incidence rates in Brazil increased by 125%, according to the results from a previous study from our group [22], the yearly number of PD procedures rose only 37% in the period. One of the factors that may have limited the expected increase in the number of PDs for PC regards to recent changes in the number and distribution of hospital beds in Brazil. In fact, there has been an absolute decrease of 8.6% in the total number of hospital beds, and of 12.7% in beds of the Health National Public System (SUS), since 2005 [34]. Moreover, we also speculate that the improvement in the accessibility to health services and the ability to perform the diagnosis of PC has not been sufficiently coordinated with investments in the medical centers and personnel to provide the surgical treatment, in face of the recently increasing demand.

Controversial results on general PD outcomes have persisted throughout the last decades [35,36]. Nevertheless, it is well accepted that careful patient selection, advances in operative technique and perioperative care have rendered pancreatic resection safer, even for the elderly [37]. Volume-outcome relationships between the number of PDs performed annually both by the institution and the surgeon have been well established in several studies [28,29,38]. Of note, a meaningful inverse correlation was reported between the number of surgeries and the associated morbidities and outcomes [39], besides preventing excessive cost and less efficient care [40]. However, there are considerable variations among centers worldwide and between low-volume and high-volume institutes of different countries [13,20,29].

Albeit the absence of a national health policy in the matter, this study reveals a trend towards regionalization of PD for PC in Brazil, which probably reflects the integration of municipalities to metropolitan regions. Also, it appears that the volume-outcome relationship for PD may occur, since LMIM concentrated by far the number of PDs performed (>50%). These cities also had the more stable PD mortality rates throughout the period (11.8% in 2015), although rates are still high in comparison to high-volume centers worldwide. Our results support some previous Brazilian studies that reported low mortality rates in patients who underwent PD in single centers; all of them located in large-sized metropolitan integrated cities of the south and southeast regions [41–45]. With regards to surgical treatment and patient's age, this study showed that the majority of PDs in Brazil were performed in patients aged 50–69 years. A trend of increasing PD among male older patients with PC was identified over the last 2 years. On the other hand, it is interesting to highlight the fact that advanced age was not a predictor for in-hospital mortality after PD. As expected, the overall mortality in the elderly was remarkably high, but the rate was relatively lower among the patients who underwent PD compared to the ones not submitted to the operative treatment, in the same age group. Similar results have been observed in a recent study from another high-volume Brazilian center [46]. This nationwide population-based study is the first to examine the rates and mortality of PD for PC in Brazil. The population-based design, with data collected from the National Health Informatics Database (DATASUS) is one of its strongest points. DATASUS collects public hospital records of each Brazilian municipality, providing the most confident official data of public health in the country. However, some limitations of this study are probably related to potential discrepancies of the available data due to local inequalities of the health care system and notification quality, particularly more relevant in the less developed areas of the country. In addition, patients and

**Table 1**
Distribution of pancreaticoduodenectomy and mortality rates according to urban and rural demographic data in Brazil, 2008–2015.

| Municipalities | 2008 | | 2009 | | 2010 | | 2011 | | 2012 | | 2013 | | 2014 | | 2015 | | PD (*n*) 2008–2015 | PD (%) | Changes in Mortality 2008–2015 (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Deaths | Mortality (%) | Deaths | Mortality (%) | Deaths | Mortality (%) | Deaths | Mortality (%) | Deaths | Mortality (%) | Deaths | Mortality (%) | Deaths | Mortality (%) | Deaths | Mortality (%) | | | |
| Integrated to metropolitan regions | | | | | | | | | | | | | | | | | | | |
| Small-sized | 0/7 | 0 | 0/5 | 0 | 0/1 | 0 | 0/3 | 0 | 4/6 | 66.7 | 0/3 | 0 | 0/2 | 0 | 1/4 | 25.0 | 31 | 1.3 | 25 |
| Medium-sized | 2/20 | 10.0 | 1/11 | 9.1 | 4/14 | 28.6 | 2/6 | 33.3 | 5/20 | 25.0 | 4/25 | 16.0 | 5/21 | 23.8 | 0/15 | 0 | 132 | 5.6 | −100 |
| Large-sized | 17/125 | 13.6 | 25/151 | 16.6 | 28/144 | 19.4 | 24/158 | 15.2 | 21/146 | 14.4 | 16/160 | 10.0 | 19/208 | 9.1 | 24/204 | 11.8 | 1296 | 55.0 | −13 |
| Not integrated to metropolitan regions | | | | | | | | | | | | | | | | | | | |
| Small-sized | 11/46 | 23.9 | 10/55 | 18.2 | 7/48 | 14.6 | 9/37 | 24.3 | 8/49 | 16.3 | 12/54 | 22.2 | 9/44 | 20.5 | 8/44 | 18.2 | 377 | 16.0 | −24 |
| Medium-sized | 6/24 | 25.0 | 3/24 | 12.5 | 3/16 | 18.8 | 2/18 | 11.1 | 1/22 | 4.5 | 2/22 | 9.1 | 5/26 | 19.2 | 6/33 | 18.2 | 185 | 7.8 | −27 |
| Large-sized | 5/32 | 15.6 | 14/50 | 28.0 | 5/35 | 14.3 | 6/44 | 13.6 | 8/35 | 22.9 | 14/43 | 32.6 | 5/56 | 8.9 | 12/48 | 25.0 | 343 | 14.6 | 60 |

prognostic characteristics may have been different among municipalities.

In conclusion, analysis of rates and mortality of PDs performed for PC in Brazil have revealed considerable disparities over the country. Many of the trends noted in this study can be attributed to specificities of the Brazilian society, with a remarkable geographic and economic heterogeneity, including different patterns of population distribution and accessibility to health care. The most developed regions and metropolitan integrated municipalities showed both the highest numbers of PD and the lowest mortality rates for the surgical procedure. These results may have important implications for practicing surgeons as well as for developing a nationwide public health policy. A national program for optimizing the care of patients with PC should strongly reinforce the process of centralization, critical for the favorable outcomes of PDs. PD can also be considered for the Brazilian elderly, whenever they have been properly selected. Future registry studies should investigate the association between outcomes of PD and hospital volumes in Brazil. Attention should be paid to several aspects, including professional multidisciplinary training and further development of excellence centers that could provide access of every citizen to the same level of care. Most importantly, the discrepancy between the increasing PC rates and the limited number of PDs offered to the population should alert authorities and guide changes in the current health policies.

## Contributors

PSLM participated in the conception and design of the study, the acquisition, analysis, and interpretation of the data, and the drafting of the manuscript. MJPL, FHS, and EJMR participated in the acquisition, analysis, and interpretation of the data and the drafting of parts of the manuscript. LRR and SHSP participated in the conception and design of the study, analyzed and interpreted the data, and critically revised the manuscript for important intellectual content. All authors gave final approval of the submitted version of the manuscript. SHSP is the guarantor.

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## Ethical approval

Not needed.

## Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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