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Impact of age over 75 years on outcomes after pancreaticoduodenectomy

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ABSTRACT

Background: The risks associated with pancreaticoduodenectomy (PD) in elderly patients continue to be debated. The aim of our study was to assess the incidence of death and postoperative complications following PD and identify the risk factors in patients >75 y.
Study design: All patients who underwent PD between January 2000 and September 2009 were analyzed retrospectively. Patients were divided into two groups according to age (Group 1: patients aged <75 y, and Group 2: patients aged ≥75 y). Morbidity and perioperative mortality risk factors were analyzed using univariate and multivariate analyses.
Results: Among the 314 patients, 273 were included in Group 1 (sex ratio 1.4) and 41 in Group 2 (sex ratio 1). In multivariate analysis, postoperative hemorrhage (PH) (OR 6.61, IC95% [1.96; 22.31], $P = 0.002$) and age >75 y proved to be predictive factors for mortality (OR 11.04, IC95% [2.57; 47.49], $P = 0.001$). When compared with Group 1, Group 2 was associated with increased postoperative deaths (24.4% *versus* 3.66%, $P < 0.001$) and pancreatic fistulas (26.8% *versus* 13.2%, $P = 0.041$), in particular, Grade C fistulas (14.6% *versus* 4.4%, $P = 0.023$). In multivariate analysis, only PH proved to be an independent predictive factor for mortality (OR 12.9, IC95% [1.07; 155.5], $P = 0.04$).
Conclusions: PD in elderly patients aged over 75 y appears to be associated with an increased risk of postoperative death and pancreatic fistula. No single preoperative factor made it possible to predict this risk.

1. Introduction

Pancreaticoduodenectomy (PD) is the only curative treatment currently available for malignant or potentially malignant tumors of the biliary-pancreatic junction.

Despite advances in surgical and anesthetic management in specialized centers over the last two decades, PD is still associated with a mortality rate of 2%–3% and a morbidity rate of 40% [1–3]. Consequently, surgery must be performed only in the absence of more risk factors.

Advanced age is frequently considered as a limitation to pancreatic surgery despite the fact that the peak incidence of pancreatic adenocarcinomas ($87.2/10^4$) occurs at 70 y, an age generally thought to be advanced [4,5].

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In a 1994 publication, the French Association of Surgery (*Association française de chirurgie*, AFC) reported perioperative mortality and morbidity rates of 8% and 35%, respectively [6]. These results varied according to age, with the mortality rate approaching 35% in subjects over 70 y. The authors subsequently recommended avoiding surgery in patients in this age group. Two recent studies evaluating the impact of age on operative morbidity and mortality reported controversial results. In the study by Haigh *et al.* [7], age >70 y was found to be an independent prognostic factor for increased postoperative complications and deaths. In contrast, de Franco *et al.* [8] showed that compared with a younger population matched for gender, body mass index (BMI), and American Society of Anesthesiologists (ASA) score, performing PD on patients older than 70 y was not associated with increased mortality and morbidity.

In Europe and, more generally, in western countries, the population is steadily aging, and thus longevity is increasing [9]. Similarly, the definition of old age has also evolved. According to the World Health Organization (WHO), old age is defined as 65 y and over, whereas geriatricians consider 75 y and over to be the benchmark in patient management. When considering PD in patients aged 75 and over, it is essential to balance the benefits in terms of quality of life and survival time with the risks of postoperative death and serious complications.

The aim of this study was to analyze perioperative mortality and morbidity following PD in patients aged 75 and over and to identify preoperative and perioperative predictors of postoperative complications.

2. Patients and methods

2.1. Patients

All patients who underwent PD for benign or malignant conditions between January 2000 and September 2009 were retrospectively analyzed. The cohort was divided into two groups according to age: patients aged <75 y (Group 1) and patients aged ≥75 y (Group 2). The age limit defining elderly patients was set at 75 y according to commonly accepted criteria in geriatric surgery. Age distribution of patients in Group 2 is shown in Fig. 1.

2.2. Collected data

The primary outcome criterion was early postoperative mortality, defined as death during the initial hospital stay or within 30 d of surgery if the patient was discharged.

Preoperative data included general patient characteristics (age, BMI, and ASA score), principal cardiovascular risk factors (arterial hypertension, diabetes, and dyslipidemia), prior surgical history, and clinical symptoms.

Perioperative data consisted of duration of operative intervention, vascular resection when needed, concomitant abdominal surgery, and transfusion needs.

Postoperative data comprised duration of initial hospital stay, need for intensive care, surgical reoperations, and rehospitalization.

The following postoperative complications were assessed: pancreatic fistula rates classified into three groups (A, B, and C) according to the International Study Group of Pancreatic Fistula (ISGPF) criteria [10]; delayed gastric emptying graded according to International Study Group of Pancreatic Surgery (ISGPS) criteria [11] (although in our series only grades B and C were considered, since the nasogastric tube was systematically left in place for 5 d); postpancreatectomy hemorrhage, including intraluminal and extraluminal bleeding according to the ISGPS definition; biliary fistula, defined as the presence of bile in the drainage fluid; and systemic infections, defined as the association of infectious signs (fever or pain) with the need for systemic antibiotics.

Morbidity was defined as the occurrence of at least one of the above-mentioned complications.

2.3. Statistical analysis

Hospital mortality for both groups was calculated using the Kaplan-Meier method and between-group comparisons were conducted using the log-rank test.

Quantitative variables were expressed as mean ± standard deviation (SD) or median and compared using Student t-test or Wilcoxon test. Qualitative variables were expressed by number and percentage and compared by means of χ^2 or Fisher exact test, as appropriate. The significance level was set at $P < 0.05$.

Factors with $P < 0.1$ in univariate analysis were entered into a multiple logistic regression model for multivariate analyses in order to identify any independent risk factors. Statistical analysis was carried out with Sigma Plot software version 11.0 (Systat Software Inc. San Jose, California)

3. Results

3.1. Patient characteristics and perioperative data

Between January 2000 and September 2009, 314 consecutive patients underwent PD, with Group 1 (<75 y) comprising 273 patients (87%) (gender ratio: 1.4) and Group 2 (≥75 y) 41 patients (13%) (gender ratio: 1). Median age was 59 y in Group 1 compared with 79 y in Group 2 ($P < 0.001$).

Patient characteristics and surgical data are provided in Table 1. Patients from Group 2 exhibited a higher ASA score than those from Group 1 ($P = 0.006$). The number of patients who underwent surgery for pancreatic cancer was higher in Group 2, but without significant difference between both groups ($P = 0.09$). Surgical data were similar for the two groups.

3.2. Perioperative mortality

The mean hospital length of stay was 18.6 ± 12.2 d and 21.1 ± 13.2 d in Groups 1 and 2, respectively ($P = 0.21$), with a maximum of 75 d in Group 1 and 61 d in Group 2.

The postoperative actuarial survival rates in both populations are shown in Fig. 2. In Group 1, 10 patients (3.6%) died after a mean period of 25.9 d (median: 22 range: 12–38), with a significantly lower rate than that of Group 2. Indeed, in the group of patients aged ≥75 y, the death rate was 24.4% after

Table 1 – Patient characteristics and surgical data.

Parameter	Total $n = 314$	Group 1 (<75 y) $n = 273$	Group 2 (≥75 y) $n = 41$	P
Gender ratio (male/female)	1.3	1.4	1	0.29
Age (y) (median [25%; 75%], min, max)	60.8 (63 [51; 72] 20; 87)	58.2 (59 [50; 69] 20; 74)	78.2 (78 [76; 79] 75; 87)	0.001
Body mass index	23.7	23.7	23.9	0.73
Previous clinical conditions:				
Alcohol consumption	68 (21.7)	66 (24.2)	2 (4.9)	0.004
Smoking (past or present)	137 (43.6)	126 (46.2)	11 (26.8)	0.031
Arterial hypertension	89 (28.3)	72 (26.4)	17 (41.5)	0.07
Diabetes	39 (12.4)	33 (12.1)	6 (14.6)	0.83
Myocardial ischemic disease	20 (6.4)	14 (5.1)	6 (14.6)	0.048
Jaundice	141 (44.9)	115 (42.1)	26 (63.4)	0.017
Acute pancreatitis	66 (21)	66 (24.2)	0 (0)	<0.01
Biliary stent	43 (13.7)	34 (12.5)	9 (22)	0.16
Surgical procedure parameters				
Duration of operation (min)	319.8 ± 90	321 ± 90	311.4 ± 89	0.54
Pancreatic duct stenting	175 (55.7)	148 (54.2)	27 (65.9)	0.22
Vascular resection	37 (11.8)	32 (11.7)	5 (12.2)	1
Blood transfusion	127 (40.5)	105 (38.5)	22 (53.7)	0.09
Pathologic findings				
Malignant tumor	213 (67.8)	180 (66)	33 (80.4)	0.09
Pancreatic adenocarcinoma	108 (34.4)	89 (32.6)	19 (46.3)	
Malignant ampulloma	41 (13.1)	34 (12.5)	7 (17.1)	
Cholangiocarcinoma	27 (8.6)	22 (8)	5 (12.2)	
Other malignant tumor	37 (11.7)	35 (12.9)	2 (4.8)	
Benign tumor	101 (32.2)	93 (34)	8 (19.6)	0.09
Chronic pancreatitis	36 (11.5)	34 (12.5)	2 (4.9)	
Other benign tumor	65 (20.7)	59 (21.5)	6 (14.7)	

Quantitative variables expressed as mean ± standard deviation (SD) or median; qualitative variables expressed as *n* (%).

a mean period of 14.6 d (median: 12 [6; 21]), with the difference in death rates between both groups achieving statistical significance ($P < 0.001$).

In Group 2, 63.4% of the patients experienced at least one complication compared with 53.5% in Group 1, with no significant difference observed between both groups ($P = 0.31$). The rate of patients admitted to the intensive care unit (20.2% *versus* 24.4%, in Groups 1 and 2, respectively; $P = 0.68$) and the rate of rehospitalization (8.4% *versus* 12.2%, respectively; $P = 0.39$) did not significantly differ between the two groups.

Postoperative complications for both groups are provided in Table 2. The incidence of complications was not influenced by the preoperative ASA score, as shown in Table 3.

3.3. *Identification of mortality risk factors in the entire population*

The overall mortality rate was 6.4%. In univariate analysis, age ($P < 0.001$), jaundice ($P = 0.01$), duration of surgery ($P = 0.008$), vascular resection ($P = 0.02$), and blood transfusion ($P = 0.01$)

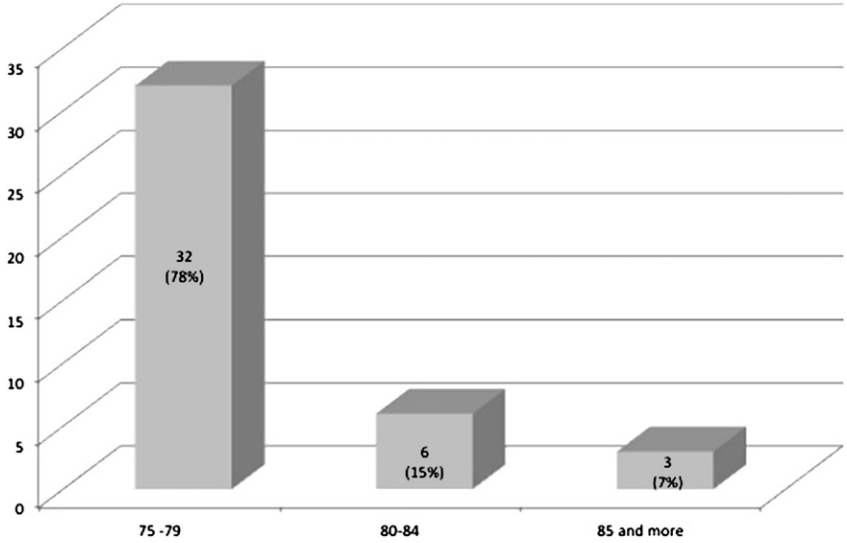

Fig. 1 – Age distribution of patients in Group 2.

Table 2 – Postoperative complications.

Parameter	Total $n = 314$	Group 1 (<75 y) $n = 273$	Group 2 (≥75 y) $n = 41$	P
Delayed gastric emptying	102 (32.5)	86 (31.5)	16 (39)	0.43
Grade B	56 (17.8)	48 (17.6)	8 (19.5)	0.93
Grade C	46 (14.7)	38 (13.9)	8 (19.5)	0.48
Pancreatic fistula	47 (15)	36 (13.2)	11 (26.8)	0.04
Grade A	0	0	0	
Grade B	29 (9.2)	24 (8.8)	5 (12.2)	0.56
Grade C	18 (5.7)	12 (4.4)	6 (14.6)	0.02
Postoperative hemorrhage	43 (13.7)	35 (12.8)	8 (19.5)	0.36
Biliary fistula	10 (3.2)	8 (2.9)	2 (4.9)	0.63
Acute pancreatitis	15 (4.8)	12 (4.4)	3 (7.3)	0.43
Abdominal collection	44 (14)	37 (13.6)	7 (17.1)	0.71
Systemic infection	106 (33.8)	91 (33.3)	15 (36.6)	0.81
Morbidity	172 (54.8)	146 (53.48)	26 (63.4)	0.31

Qualitative variables expressed as *n* (%).

were all associated with an increased risk of postoperative death (Table 4).

Delayed gastric emptying, pancreatic fistula rates, and postoperative hemorrhage rates were found to be significantly higher in patients who died compared with those who survived ($P = 0.01$, $P = 0.004$, and $P < 0.001$, respectively). Similarly, postoperative pancreatitis, abdominal collection, and systemic infection rate were significantly increased in patients who died ($P = 0.001$, $P = 0.045$, and $P < 0.001$, respectively).

In multivariate analyses, age and postoperative hemorrhage were the only factors still significantly associated with an increased mortality risk (Table 4).

3.4. *Identification of mortality risk factors in Group 2*

In univariate analysis, male gender ($P < 0.032$), prolonged surgical duration ($P = 0.044$), reoperation ($P < 0.001$), and transfer to intensive care ($P < 0.001$) were significantly associated with an increased risk of postoperative death (Table 5).

Pancreatic fistula rates were significantly higher in patients who died than those who survived (60% *versus* 16.13%; $P = 0.013$), particularly in terms of Grade C fistulas (60% *versus* 0% in dead and surviving patients, respectively; $P < 0.001$). Similarly, postoperative hemorrhage rates were found to be significantly higher in patients who died compared with those who survived (60% *versus* 6.45%, respectively; $P = 0.001$).

In multivariate analysis, the only factor still significantly associated with an increased mortality risk was the occurrence of postoperative hemorrhage ($P = 0.044$; OR = 12.9, IC95% [1;155]).

4. Discussion

At the beginning of the 21st century, there were approximately 600 million elderly people worldwide, i.e., three times more than 50 years ago. This number is projected to reach 2 billion by 2050, or in other words, three times more than today [12]. At the same time, the elderly population itself is aging, with the very old (≥80 y) the fastest-growing population group at an increase of 3.8% per year [12,13]. This trend obviously implies an expansion of surgical indications for increasingly older subjects. When contemplating major surgery, such as PD, in elderly patients, recent consensus-based data on morbidity and mortality are required so surgical indications

Table 3 – ASA score impact in Group 2.

Parameter	ASA 1	ASA 2	ASA 3	P
Patients, *n* (%)	3 (7.3)	27 (65.9)	11 (26.8)	
Male gender, *n* (%)	1 (33.3)	11 (40.7)	8 (72.7)	0.18
Age	77.3	78.3	8.4	0.87
Operative parameters				
Duration of operation (min ± SD)	260 ± 36	316.4 ± 95	314.4 ± 87	0.6
Patients transfused, *n* (%)	1 (33.3)	16 (59.3)	5 (45.5)	0.53
Postoperative complications				
Delayed gastric emptying, *n* (%)	3 (100)	9 (33.3)	4 (36.4)	0.12
Pancreatic fistula, *n* (%)	1 (33.3)	7 (25.9)	3 (27.3)	1
Postoperative hemorrhage, *n* (%)	1 (33.3)	3 (11.1)	4 (36.4)	0.19
Mortality, *n* (%)	1 (33.3)	6 (22.2)	3 (27.3)	
Length of hospital stay, mean (d) ± SD	30.3 ± 26	18 ± 9	26.5 ± 16	0.09

Table 4 – Univariate and multivariate analyses identifying predictive morbidity factors in all patients.

Parameter	Univariate analysis			Multivariate analysis	
	Patients deceased $n = 20$	Patients alive $n = 294$	*P* value	Odds ratio (95% CI)	*P* value
Gender (male)	13 (65)	126 (42.8)	0.09	2.38 (0.52; 10.94)	0.267
Age (y)			<0.001	11.04 (2.57; 47.49)	0.001
<75	10 (24.4)	31 (75.6)			
≥75	10 (3.7)	263 (96.3)			
BMI	25.49	23.63	0.07	1.11 (0.96; 1.28)	0.141
Jaundice	15 (75)	126 (42.9)	0.01	0.87 (0.22; 3.42)	0.841
Duration of operation (min ± SD)	385 ± 88	317 ± 89	0.008	1.01 (0.99; 1.01)	0.167
Vascular resection	6 (30)	31 (10.5)	0.02	1.59 (0.27; 9.19)	0.608
Blood transfusion	14 (70)	113 (38.4)	0.01	2.45 (0.55; 10.99)	0.241
Delayed gastric emptying	12 (60)	90 (30.6)	0.01	1.52 (0.48; 5.29)	0.51
Pancreatic fistula	8 (40)	39 (13.3)	0.004	1.32 (0.32; 5.48)	0.707
Grade C	8 (40)	10 (3.4)	<0.001		
Postoperative hemorrhage	11 (55)	32 (10.9)	<0.001	6.61 (1.96; 22.31)	0.002
Postoperative pancreatitis	5 (25)	10 (3.4)	0.001	3.03 (0.56; 17.5)	0.215
Abdominal collection	6 (30)	38 (12.9)	0.045	0.69 (0.16; 3.04)	0.623
Systemic infection	15 (75)	91 (31)	<0.001	3.07 (0.80; 11.79)	0.102

Quantitative variables expressed as mean ± SD or median; qualitative variables expressed as *n* (%).

can be defined without compromising patient life expectancy and quality of life.

In our study, perioperative mortality following PD was found to be higher in patients aged ≥75 y than in patients aged <75 y (24% *versus* 3.4%, $P = 0.001$). These results are in line with the findings of Gouma *et al.* [14] and Haigh *et al.* [7], who respectively demonstrated that the ages of 65 and 70 were associated with an increased risk of perioperative mortality. In contrast, de Franco *et al.* [8] did not find any difference in terms of mortality between patients aged ≥70 y and their control group. Recently, Khan *et al.* [15] showed that with identical ASA scores, complication rates were higher and hospital stays longer in elderly subjects undergoing PD when compared with young subjects. Our results did not confirm these data since no significant increase in overall morbidity or in the main postoperative parameters was observed in patients aged ≥75 y, with the exception of the pancreatic fistula rate, particularly ISGPF Grade C, which was significantly higher in this older age group. To our knowledge, this last finding has not been reported since age was not considered to be a predictor for fistula occurrence [16–18]. These fistulas could have been linked to an altered microvascularization in the elderly as well as their frequently altered nutritional status. As for the other postoperative parameters, such as delayed gastric emptying, age did not appear to have any impact, as previously suggested by Scurtu *et al.* [19].

PD can therefore be performed in patients aged ≥75 y while taking into account their physiologic status, which may not properly adjust to even minor complications, thereby resulting in an increased mortality risk. In fact, our results revealed that in univariate analysis, postoperative complications in older patients were associated with significantly increased mortality. However, this increased postoperative mortality can be observed following any major surgery. In particular, in colorectal surgery, which is probably the most studied surgery in elderly patients, the mortality risk increases by 3.2 times between the ages of 75 and 84 y and by 6.2 times after the age of 85 y [20]. Similar results have been reported for

Table 5 – Univariate and multivariate analyses identifying predictive factors of morbidity in Group 2.

Parameter	Univariate analysis			Multivariate analysis	
	Patients deceased $n = 10$	Patients alive $n = 31$	*P* value	Odds ratio (95% CI)	*P* value
Gender (male)	8 (80)	12 (38.7)	0.03	2.19 (0.17; 28.07)	0.55
Age (y)	79.5 [78; 80]	77 [76; 79]	0.02	1.17 (0.78; 1.75)	0.46
Duration of operation (min ± SD)	378.3 ± 70	298.4 ± 88	0.04	1.01 (0.99; 1.02)	0.08
Vascular resection	3 (30)	2 (6.45)	0.08	2.56 (0.09; 77.4)	0.59
Pancreatic fistula	6 (60)	5 (16.1)	0.013	3.87 (0.31; 47.8)	0.29
Grade C	6 (60)	0 (0)	<0.001		
Postoperative hemorrhage	6 (60)	2 (6.45)	0.001	12.9 (1.07; 155.47)	0.04
Abdominal collection	4 (40)	3 (9.68)	0.047	0.91 (0.02; 29.08)	0.96
Systemic infection	8 (80)	7 (22.6)	0.002	2.56 (0.16; 42.19)	0.51

Quantitative variables expressed as mean ± SD or median; qualitative variables expressed as *n* (%).

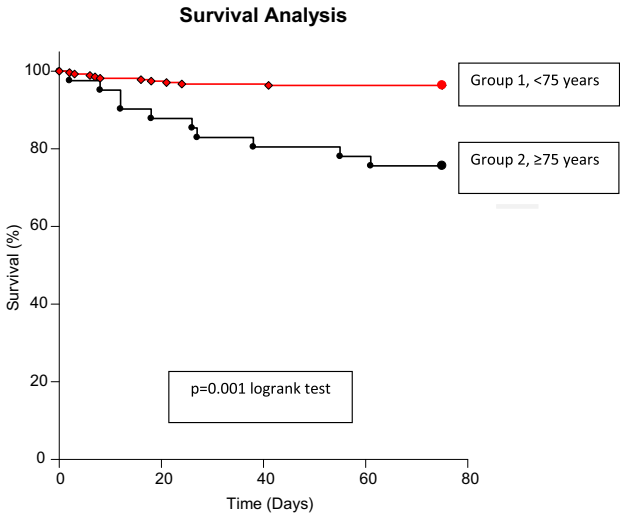

Fig. 2 – Survival curves for the two patient groups using the Kaplan-Meier method. (Color version of figure is available online.)

hepatobiliary surgery, with mortality rates increasing between 2.9 and 6.7 times in subjects over the age of 75 [21].

The difficulties inherent in gerontosurgery are related to estimating the physiologic status of patients. These patients, who often present multiple pathologic conditions, are at a higher risk of developing rapid malnutrition and infections, or experiencing the impact of preoperative and postoperative hypovolemia. Given this context, our study revealed the occurrence of postoperative hemorrhage following PD as an independent risk factor for mortality. One explanation could be that preoperative coronary insufficiency was significantly more common in Group 2 patients, who were consequently less likely to tolerate anemia or hypovolemia and secondary ischemia caused by bleeding.

Several remarks should be made concerning these observations. First, surgical expertise appears to be of paramount importance since it has been shown to reduce postoperative complications following PD [1,2,22] and, thus, the necessity for managing patients in high-volume centers. Second, the risk of postoperative coronary accidents should be accurately estimated using the Lee score [23], which should be routinely undertaken in this patient population.

In our series, increased ASA scores prior to surgery were not linked to higher mortality rates, in contrast with the data published by Adam *et al.* [24]. This could be explained by the fact that among the elderly group, no patient presented an ASA >3, since such patients are usually excluded from PD surgery. This score, which is widely and often exclusively used, proved not to be sensitive enough for elderly patients. Therefore, more specific scores should be employed for the elderly in order to better select patients eligible for PD without increased risk of death. Prior to performing PD surgery, it is much more important to take into account the physiologic age of patients rather than their chronological age by using geriatric indices, such as the Charlson score [25,26], Cumulative Illness Rating Scale, or Kaplan-Feinstein index [27]. These geriatric indices have proven to be simple, reliable, and sensitive when used during preoperative consultation, with the Charlson score the most commonly used in the cancer patient setting [27].

To conclude, our study revealed PD performed in patients aged ≥75 to be associated with increased risk of mortality and pancreatic fistulas. In this patient group, we were unable to identify preoperative predictors of death or early postoperative complications. In practice, the decision to perform surgery or not should not be based only on chronological age, but rather patients should be selected on the basis of geriatric indices shown to be more reliable than age and ASA score. For this patient group, performing surgical resections at a specialized center appears to be the best means to decrease the risk of postoperative complications.

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