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Impact of postoperative complications on clinical and economic consequences in pancreatic surgery

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Purpose: Patients who develop complications consume a disproportionately large share of available resources in surgery; therefore the attention of healthcare funders focuses on the economic impact of complications. The main objective of this work was to assess the clinical and economic impact of postoperative complications in pancreatic surgery, and furthermore to assess risk factors for increased costs.
Methods: In all, 161 consecutive patients underwent pancreatic resection. The costs of the treatment were determined and analyzed.
Results: The overall morbidity rate was 53.4%, and the in-hospital mortality rate was 3.7%. The median of costs for all patients without complication was 3,963 Euro, whereas the median of costs for patients with at least one complication was significantly increased at 10,670 Euro ($P < 0.001$). In multivariate analysis American Society of Anesthesiologists ≥ 3 ($P = 0.006$), multivisceral resection ($P < 0.001$) and any complication ($P < 0.001$) were independently associated with increased costs.
Conclusion: Postoperative complications are associated with an increase in mortality, length of hospital stay, and hospital costs. The treatment costs increase with the severity of the postoperative complications. Those factors that are known to increase the treatment costs in pancreatic resection should be considered when planning patients for surgery.
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Key Words: Pancreaticoduodenectomy, Pancreatectomy, Postoperative complications, Pancreatic fistula

INTRODUCTION

The mortality associated with pancreatic resection has decreased rapidly in the past decades due to the refinement of operative technique, introduction of new materials and surgical devices, and improvement in postoperative care, including mini-invasive radiology techniques [1-3]. However, the morbidity associated with pancreatic resections remains high, up to 50%. The most serious postoperative complications include postoperative pancreatic fistula (POPF), delayed gastric emptying, postoperative bleeding, and infectious complications [4,5].

Healthcare expenditure is currently rising exponentially, including in surgical fields. One of the reasons for this is the use of new surgical techniques and devices. However, postoperative complications are the main reason for increased costs in surgery [6]. Patients who develop complications consume a disproportionately larger share of the available resources [7]. Moreover, postoperative morbidity may not only increase the costs of care, but may also lead to prolonged sick leave or even to permanent incapacity [7]. Since healthcare resources are limited, the funders of healthcare should know how complications increase the cost of the treatment.

Several studies have shown that POPF, as the most ominous

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complication after pancreatic resection, increases the cost of treatment and has severe clinical consequences as well [1,3,8]. Resources are limited, with healthcare expenditure accounting for 7.8% of the gross domestic product in the Czech Republic. Hence the attention of healthcare funders (government and insurance companies) must focus on the precise economic impact of the quality of healthcare delivery.

Few scoring systems exist for postoperative complications [9-12]; they may offer tools for calculating the economic impact of a procedure based on the severity of the postoperative course. A therapy-oriented complication scoring system ranking complications by severity into 5 grades was developed by Dindo-Clavien [13], and has been modified for pancreatic surgery [5]. Unlike other scoring systems like POSSUM (Physiological and Operative Severity Scoring System for Enumeration of morbidity and Mortality) and its Portsmouth modification (P-POSSUM), the Dindo-Clavien classification is kept simple and easy to use without any additional calculations [13].

Cost analysis of major surgical procedures was published by Vonlanthen et al. [6] in 2011. This study included 1,200 patients undergoing elective liver, pancreas, colorectal and Roux-en-Y gastric bypass over a period of 4 years. It assessed the hospital costs between the procedures for uncomplicated and complicated postoperative courses. The study revealed that pancreatic surgery is different from other surgical procedures. The costs of pancreatic surgery were significantly higher compared with all other procedures, and the difference was even greater in patients with complications [6]. Based on the results of this study, we decided to study the financial consequences of complications in pancreatic surgery in greater detail.

The main objective of this work was to assess the clinical and economic impact of postoperative complications in pancreatic surgery. A secondary goal was to validate the classification of complications in terms of their economic and clinical consequences. A third goal was to assess risk factors for increased costs in pancreatic surgery.

METHODS

Hospital records from patients who underwent elective pancreatic resection from January 2007 through June 2013 in a single tertiary care center were identified from our prospectively entered pancreatic surgery database; all the data was therefore collected prospectively. One hundred sixty-one elective pancreatic resections were performed in this period. The study was reported according to the STROBE (strengthening the reporting of observational studies in epidemiology) statement [14].

Surgical technique

The surgical technique has been previously reported [1]. Briefly, following the pancreaticoduodenectomy, a pancreaticojejuno anastomosis was constructed in end-to-side fashion. Ductal stents were never used, and pancreaticogastrostomy was never performed. Open distal pancreatectomy was performed in a uniform fashion. Sharp transection was performed with a blade in a "fish-mouth" fashion. If the main pancreatic duct was visible, it was occluded with a stitch; afterwards, the pancreatic remnant was secured with manual sutures. No staplers were used for the transection of the pancreas in the open procedure. For laparoscopic pancreatic resection, the transection was performed with a stapler. Prophylactic octreotide was given to all patients (100 μg every 8 hours) and continued for 5 days. Prophylactic antibiotics were started 30 minutes before operation and continued for 48 hours.

Postoperative management was standardized for all patients. Outputs from all drains were recorded daily. The amylase concentration was measured every other day starting on postoperative day 3. The drains were removed based on the amylase concentration and volume of the drainage output. In clinically suspicious cases, ultrasound or CT scans were performed to assess peripancreatic fluid collections or other postoperative complications. Undrained collections associated with clinical (abdominal discomfort, fever, abdominal pain) or laboratory abnormalities (increased WBC, increased CRP) were drained with CT guidance.

Definitions of pancreatic fistula and morbidity

Pancreatic fistula was defined according to the International Study Group for Pancreatic Fistula (ISGPF) as output via operatively or postoperatively placed drains of any measurable volume of drain fluid on or after postoperative day 3, with amylase content greater than three times the upper normal serum value. Three grades of pancreatic fistula were determined according to their clinical severity [15]. All other postoperative complications were assessed according to the grading system proposed by Dindo-Clavien [13] and DeOliveira et al. [5] .

Data collection and outcome measures

All of the data were prospectively entered into the pancreatic surgery database in our department. Preoperative parameters included basic patient demographics (age, gender, and comorbidity) and presenting symptoms. Intraoperative parameters included operative time, perioperative complications, and blood loss. Postoperative events and management included incidence and type and severity of complication, intensive care unit (ICU) stay, total hospital stay, radiological interventions, reoperations, and mortality. Patients were divided according to the most severe complication, represented by the most relevant clinical event [13]. Death of the patient

was included if it occurred within 30 days after the surgical procedure or within the same hospital stay.

Cost calculations

The economic consequences of complications were determined by the cost of the treatment during the hospital stay and during the out-patient follow-up period, lasting until all the complications were resolved and the patient was completely healed. Cost data was provided by the financial department of the hospital. Hospital costs included operating room, pharmacy (medications, fluid management, and nutritional support), radiology (all imaging studies and interventional radiology), transfusion (blood products), laboratory, ICU, and room costs. All costs are expressed in Euro. Results are expressed as median and interquartile range (IQR).

Statistical analysis

Descriptive analysis of patient characteristics, outcomes, and postoperative complications was performed. Respecting the fact that the costs were non-normally distributed, we used the median and IQR for the description of the costs. Calculated costs without transformation led to regression models that violated the assumption of normally distributed data. Hence, we used the natural logarithm of the costs for further calculation; the regression model fulfilled the assumption of linear regression. The suitability of this model was assessed as appropriate, with adjusted R^2 (determination coefficient) 0.521. A similar method was described by Vonlanthen et al. [6].

Analysis of complications was performed using the chi-square test, and the Fisher exact test. The Kruskal-Wallis nonparametric analysis of variance was used to analyse the treatment costs. *Post hoc* comparison of hospital costs for various complication grades was performed using Dunn test with Bonferonni adjustment.

Using multivariate linear regression, we then assessed which parameters (age, American Society of Anesthesiologists [ASA] score ≥ 3, body mass index ≥ 30 kg/m^2, preoperative diabetes and ischemic heart disease, operating time ≥ 300 minutes, blood loss over 1,000 mL, type of procedure, and multivisceral resection) predicted increased hospital costs. Finally, we used the nonparametric Mann-Whitney and Kolmogorov-Smirnov tests to analyze which types of complications are responsible for the biggest increase in treatment cost. Statistical significance was set to $P < 0.05$. Statistical analyses were performed using statistical software NCSS 9 (NCSS, Kaysville, UT, USA).

RESULTS

All patients met the criteria for the evaluation and analysis. Patients' characteristics are shown in Table 1. Eighty-six patients had one or more postoperative complications; the overall morbidity rate was 53.4%. Sixty patients had a fistula for an overall POPF incidence 37.3%; 23 patients had POPF grade A (14.3%), 29 had POPF grade B (18.0%), and 8 had POPF grade C (5%). The 30-day mortality rate was 1.2% (2 patients); overall in-hospital mortality rate was 3.7% (6 patients). Percutaneous drainage of peripancreatic collections under CT guidance was required in 12 patients (7.5%); interventional angiography with embolization of a bleeding source was performed in 3 patients (1.9%). Reoperations were performed in eight patients (5%): in five because of POPF grade C, and for postoperative bleeding in 3. Patients who suffered complications had an increased median of ICU stay (5 days *vs.* a median of 3 days for patients without complications, and IQR, 3–8.25 days *vs.* 2–4 days, $P < 0.05$) and overall hospital stay (19.5 days *vs.* a median of 11 days; and IQR, 14–32.75 days *vs.* 9–14 days; $P < 0.05$).

Cost analysis

The overall median of hospital costs for the whole population studied was 4.961 Euro (IQR, 3.788–6.650 Euro). The median of treatment costs of all patients without complication was 3.963 Euro (IQR, 2.915–4.836 Euro), whereas the median of costs of patients with at least one complication was 6.404 Euro (IQR, 4.903–8.852 Euro), a significant increase ($P < 0.001$). We further analyzed the impact of complication severity on the costs. Grade 1 complication created an additional cost of 635 Euro (IQR, –597–1,827 Euro) compared to patients without complications; for grade 4 the additional cost reached 28,751 Euro (IQR, 18,536–39,807 Euro).

The economic consequences of complications are analyzed in Table 2. Comparing the total hospital costs for both procedures without complications, the table shows that hospital costs for pancreaticoduodenectomy is higher than for distal pancreatectomy (4,403 Euro *vs.* 2,934 Euro, $P < 0.001$). However, analyzing the cost of the treatment for both procedures with complications Grade 2 and higher, we can see that there is no difference between the procedures ($P = 0.604$). We then analyzed the costs of treatment for both procedures together with complications. The median of total treatment costs increased through the complication grades. Dunn test with Bonferonni adjustment shows the comparison of hospital costs for various complication grades in Table 3. A strong association between the severity of the complications and the treatment costs was observed.

In the univariate analysis of predictors of costs, the significant predictors were age ≥ 70 years (*vs.* <70 years, $P = 0.016$), ASA score ≥ 3 (*vs.* <3, $P < 0.001$), male sex (*vs.* female sex, $P = 0.01$), operating time > 300 minutes (*vs.* <300 minutes, $P < 0.001$), blood loss > 1,000 mL (*vs.* <1,000 mL, $P = 0.031$), preoperative ischemic heart disease ($P = 0.011$), multivisceral resection ($P < 0.001$), any postoperative complication (*vs.* no complications, $P < 0.001$). In multivariate analysis only ASA ≥ 3 ($P = 0.006$),

Table 1. Patients' characteristics

Characteristic	No complications (n = 75)	Complications (n = 86)	P-value
Age (yr)	60.8 ± 11.7	64.8 ± 10.1	0.024
Sex			
Male:female	30:45	44:42	0.156
ASA score			0.002
I	7 (9.3)	3 (3.5)	
II	52 (69.3)	42 (48.8)	
III	16 (21.4)	40 (46.5)	
IV	0 (0)	1 (1.2)	
Body mass index (kg/m^2)	26.7 ± 4.3	26.8 ± 4.3	0.708
<25	33 (44)	38 (44.2)	0.971
26–30	29 (38.7)	32 (37.2)	
>31	13 (17.3)	16 (18.6)	
Preoperative diabetes	14 (18.7)	20 (23.3)	0.477
History of ischemic heart disease	8 (10.7)	15 (17.4)	0.220
Histology findings			<0.001
Pancreatic adenocarcinoma	35 (46.7)	27 (31.4)	
Cystic tumors	12 (16)	14 (16.3)	
Carcinoma of the papilla of Vater	7 (9.3)	15 (17.4)	
Carcinoma of distal bile duct	1 (1.3)	6 (7)	
Endocrine tumor	10 (13.4)	3 (3.5)	
Chronic pancreatitis	4 (5.3)	8 (9.3)	
Other	6 (8)	13 (15.1)	
Pancreaticoduodenectomy	(n = 42)	(n = 66)	
Whipple/Traverso-Longmire	16/26	34/32	0.173
Surgery time	305 (275–338)	305 (270–340)	0.744
Blood loss	600 (500–1,000)	600 (500–800)	0.649
Hospital stay	12 (11–14)	20.5 (15–33)	<0.001
ICU stay	3.5 (2–4)	5.5 (4–11)	<0.001
Distal pancreatectomy	(n = 33)	(n = 20)	
With splenectomy/spleen-preserving	11/22	7/13	0.901
Surgery time	185 (145–213)	220 (196–276)	0.008
Blood loss	500 (325–600)	500 (400–600)	0.642
Hospital stay	10 (8.5–13.5)	16 (11–39)	0.002
ICU stay	2 (1–3.5)	4 (2–6)	0.022

Values are presented as mean±standard deviation, number (%), or median (range).
ASA, American Society of Anesthesiologists; ICU, intensive care unit.

Table 2. Cost (Euro) of treatment

Complication	Total	Hospital stay (day)	Pancreaticoduodenectomy	Distal pancreatectomy
No complication	3,963 (2,915–4,836)	11 (9–14)	4,403 (3,855–5,184)	2,934 (2,563–3,987)
Grade 1	4,598 (3,366–5,790)	14 (12–16)	5,221 (3,844–6,413)	2,831 (2,278–4,630)
Grade 2	6,257 (5,213–8,363)	20 (15–25)	6,037 (5,209–8,369)	6,551 (5,571–8,530)
Grade 3	7,719 (5,971–11,381)	27.5 (16.5–56)	7,199 (6,175–9,656)	8,238 (4,474–12,094)
Grade 4	32,713 (22,499–43,771)	63.5 (52–78)	33,760 (20,654–46,300)	31,666
Grade 5	35,287 (25,821–59,571)	46.5 (23–78.5)	32,288 (25,821–59,571)	-

Values are presented median (interquartile range).

multivisceral resection ($P < 0.001$) and any complication ($P < 0.001$) were independently associated with increased costs. The results are summarized in Table 4.

Finally, the impact of the type of complication was analyzed using the Mann-Whitney and Kolgomorov-Smirnov tests. The largest differences between the hospital costs were seen

Table 3. *Post hoc* comparison of treatment costs using the Dunn test with Bonferonni adjustment

Complication	No complication	Grade 1	Grade 2	Grade 3	Grade 4	Grade5
No complication	0	NS	P < 0.001	P < 0.001	P < 0.001	P < 0.001
Grade 1		0	P < 0.05	P < 0.01	P < 0.001	P < 0.001
Grade 2			0	NS	P < 0.05	P < 0.05
Grade 3				0	NS	NS
Grade 4					0	NS
Grade 5						0

NS, not significant.

Table 4. Risk factors for increased costs

Variable	Univariate		Multivariate	
	Standardized beta	P-value	Standardized beta	P-value
Age >70 yr	0.1905	0.016	–0.0292	0.647
ASA ≥3	0.3697	<0.001	0.1984	0.006
Body mass index >30 kg/m^2	–0.1230	0.120	–0.1063	0.083
Sex (female ref)	0.2026	0.010	–0.0097	0.876
Operating time >300 min	0.3136	<0.001	0.0854	0.216
Blood loss >1,000 mL	0.1704	0.031	0.1148	0.064
Preoperative diabetes	0.1234	0.119	0.0086	0.885
Ischemic heart disease	0.2012	0.011	0.0670	0.303
Multivisceral resection	0.2797	<0.001	0.3274	<0.001
Complication 1–5 (0 ref)	0.503	<0.001	0.3437	<0.001

ASA, American Society of Anesthesiologists.

in cardiovascular complications, followed by postoperative haemorrhage and pneumonia (Table 5). Only urinary tract infection had no impact (P = 0.305).

DISCUSSION

With gradual improvement in surgical technique and mini-invasive procedures such as interventional radiology and endoscopy, mortality of pancreatic resection has dropped significantly; however, morbidity remains high. This study confirms the current trend in pancreatic resections – high morbidity up to 50% [5], with some series reporting morbidity of 75% [6], and low mortality (in-hospital mortality in our series 3.7%). The postoperative morbidity rate depends largely on the definition of postoperative complications [13]. It is the same situation as with the POPF rate which largely depends on POPF definition [16]. When the various definitions of POPF are applied to identical groups of patients, the rate of pancreatic fistula can range from 10% to 29% according to which definition is applied [16]. Naturally, a broad POPF definition will result in higher POPF rates [15,16]. Likewise a broad definition of morbidity will result in a higher postoperative morbidity rate [5,7,13].

Complications cannot be graded simply as "minor" or "major", and "surgical" or "nonsurgical" [17]. Specific grading of complications, e.g., proposed by Dindo-Clavien, should be used so that the results can be compared within the same institution over time and also among different institutions [13]. A precise and convincing outcome assessment is needed as a surrogate marker for medical quality; pressure for assessing the quality of care comes from patients and the funders of healthcare so that they can compare the quality of centres and this will inevitably increase in the future.

Many papers report in terms of 30-day mortality [3,18]. However, with modern intensive care facilities, mini-invasive endoscopic and interventional radiologic procedures, new medications, and better organ support, patients often survive more than 30 days after the surgical procedure even with very serious complications, but succumb after 30 days due to postoperative complications. Therefore, in-hospital mortality is more accurate and should be used instead of 30-day mortality [18]. In this series, the 30-day mortality rate was 1.2% (2 patients) and the overall in-hospital mortality rate was 3.7% (6 patients).

The definition of POPF by the ISGPF is well established, repeatedly reported in the literature and confirmed by other series [1,3,19]. However, even this definition has its limitations. By its nature, the grade of severity of POPF according to the ISGPF can be determined only after healing of the fistula [15]. The ISGPF definition cannot be used prospectively in decision-making during the treatment of the fistula, and it is not capable of distinguishing between clinically significant and nonsignificant fistulae [2]. Some authors argue that the ISGPF grading system includes multiple subjective criteria that are highly dependent on subjective impressions made by the treating surgeons, and is not applicable to other complications [5]. However, the ISGPF definition has been widely accepted

Table 5. Total hospital costs (Euro) for patients with and without various types of complications

Complication	No.	Complication present	Complication absent	P-value
Pancreatic fistula	60	6,479 (4,590–9,500)	4,329 (3,186–5,370)	<0.001
Delayed gastric emptying	16	14,977 (6,669–32,148)	4,692 (3,571–6,117)	<0.001
Postoperative hemorrhage	17	22,553 (6,496–33,091)	4,744 (3,568–6,053)	<0.001
Wound infection	14	8,700 (5,503–14,605)	4,821 (3,731–6,469)	0.003
Pneumonia	10	20,655 (7,884–45,028)	4,761 (3,731–6,457)	<0.001
Intra-abdominal abscess	22	8,635 (5,459–25,085)	4,685 (3,544–6,058)	<0.001
Urinary tract infection	8	7,021 (4,023–11,442)	4,922 (3,778–6,528)	0.305
Cardiovascular	12	32,044 (9,694–40,469)	4,726 (3,654–6,264)	<0.001
Neurological	9	6,353 (5,262–16,052)	4,829 (3,740–6,540)	0.018

Values are presented mean (interquartile range).

[19,20], is used in most of the currently reported series nowadays [21], and can serve in comparing results within a single institution over time or among various institutions. We therefore used the ISGPF definition in this series as well. Other complications besides POPF can be defined and graded as proposed by Dindo-Clavien. This definition of complications has also been widely accepted and confirmed on a large series of patients [6].

This study confirms the stratification of morbidity proposed by Dindo-Clavien [13] and DeOliveira et al. [5] regarding clinical and economic consequences. Postoperative complications are associated with increased cost of the treatment, longer ICU stay, and total hospital stay. Increased costs are associated with the severity of the complications, with the cost of treatment in patients with complications grades 2–5 being significantly higher than in patients with complication grade 1 or no complication (Table 2). The absolute numbers representing the treatment costs are probably country-specific and even centre-specific. However, the relative increase in treatment cost is valid irrespective of the location. The two most common types of pancreatic resection (pancreaticoduodenectomy and distal pancreatectomy) are different only when there are no complications, the cost of pancreaticoduodenectomy being significantly higher. However, where there are complications of grade 2 or higher, the cost of the treatment is then similar. This could be explained by the fact that patients who develop complications consume a disproportionately larger share of the available resources [7]. Patients with complications following both procedures require additional interventions (reoperations, endoscopic procedures, interventional radiology) and above all, very frequently, intensive care, which is one of the most costly items [1].

Regarding the type of complications, the greatest difference was seen in cardiovascular complications, followed by postoperative hemorrhage and pneumonia. These are the complications that more frequently require treatment in intensive care units, and are often associated with multiorgan failure and death (grades 4 and 5).

Similar papers relating to pancreatic resection were published by Lang et al. [7] and Vonlanthen et al. [6]. The first paper by Lang et al. [7] studied resource utilization in gastroenterological surgery. Out of 235 patients in the study, only 14 received pancreatic resection. When studying the costs of the procedures, the difference was not statistically significant (6,678 Euro with no complications *vs.* 9.168 Euro with complications, P = 0.156). This might be caused by the low number of patients included. Moreover, the authors did not use any of the definitions of postoperative complications.

The latter study by Vonlanthen et al. [6] included 1,200 patients, of whom 110 received pancreatic resection. Pancreatic surgery was the most expensive compared to liver surgery, colorectal surgery, and Roux-en-Y gastric bypass. Mean costs in US dollars ($) with standard deviation (SD) for all patients were 71,111 (78,688), 49,289 (54,529), 48,822 (66,564), and 29,689 (18,171), respectively. In pancreatic surgery, the mean cost without complications was significantly lower compared to patients with complications (31,809 *vs.* 82,576). However, this study has several limitations. Firstly, the authors did not specify which type of pancreatic resection was included in the study, and secondly they did not specify the rate of POPF. In addition, the postoperative morbidity rate in this series was unusually high reaching 74.6% and no explanation was offered for such a high morbidity rate.

Many authors have suggested that complications should be prevented [22]. However, even with the up-to-date principles of pancreatic surgery, new devices and mini-invasive methods, complications still occur, and the complications rate may be around 50% [5] or even higher [6]. It may partly be due to the fact that surgeons tend to operate on older patients, with significant comorbidities, or on locally advanced tumors requiring resection of the porto-mesenteric venous complex or additional organs [23-25]. When a surgeon recommends patients for pancreatic resection it is very important to know the risk factors for postoperative complications, especially POPF

[4,26]. When a patient is scheduled for pancreatic resection, the factors associated with increased cost for the treatment might be already known. The risk factors for POPF [26], postoperative morbidity [4], and postoperative mortality [18,27] are all well known. However, no study has yet analyzed the risk factors for increased cost of the treatment. Even in pancreatic resections, it is not appropriate to analyze POPF alone; all complications should be studied complexly. In older patients with significant comorbidities and higher risk, other complications are more frequent than POPF alone. Studies dealing with prognostic predictors after pancreatic resection should move their focus from pancreatic fistula alone to overall major complications, which can increase mortality and translate to prolonged hospital stay and higher costs [4].

In conclusion, postoperative complications are associated with increased mortality, length of stay, and hospital costs. Modern surgical care is costly; however, patients who develop complications consume a disproportionately larger share of the available resources. This study demonstrates that treatment costs increase with the severity of postoperative complications.

The definition of complications designed by Dindo-Clavien [13], and adjusted for pancreatic surgery [5], is simple to use, is easily applied to the patient database, and is capable of stratifying the postoperative complications and analyzing the treatment costs in the various grades of complications.

Since resources for healthcare are limited, the attention of healthcare funders and patients should be focused on the economic impact of the surgical procedures. Those factors that are known to increase treatment costs in pancreatic resection should be considered when planning patients for surgery.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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