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Efficacy and safety of transpancreatic sphincterotomy in endoscopic retrograde cholangiopancreatography: a retrospective cohort study

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Abstract

Background Difficult cannulation represents a common obstacle during endoscopic retrograde cholangiopancreatography (ERCP). We assessed the efficacy and adverse events of transpancreatic sphincterotomy (TPS), and investigated potential associated confounders.

Methods All patients referred to our department for ERCP during 2015-2020 were eligible if they had intact papilla and visceral anatomy. In addition to standard measures, TPS was combined with pancreatic stent placement. Apart from demographics, we retrieved data related to the indication, periampullary anatomy, necessity for TPS or fistulotomy, their outcomes and complications. Chi-square test was employed to investigate associations between TPS and independent variables. When significance was observed, the respective variables were inserted into a regression model.

Results A total of 1082 individual patients were eligible, with an equal female: male ratio and a mean age of 72.7±15.82 years. Seventy-three patients (6.7%) underwent TPS, with a 95.9% successful cannulation rate. Papilla morphology or regional diverticulum did not affect the decision to perform TPS, though it was significantly associated with malignant common bile duct (CBD) obstruction as the ERCP indication (P=0.001). Considering adverse events, TPS did not increase the incidence of post-ERCP pancreatitis (PEP), though it affected bleeding (P=0.005). Regression analysis revealed a protective role of TPS against PEP (risk ratio [RR] 0.015, 95% confidence interval [CI] 0.23-5.05; P<0.001), while the aforementioned risk of hemorrhage was attributed to previous precut attempts (RR 3.02, 95%CI 1.42-6.43; P=0.004).

Conclusion TPS combined with pancreatic stenting is an effective and safe modality in difficult cannulation cases and could be the first-choice alternative in malignant CBD obstruction.

Keywords Transpancreatic sphincterotomy, endoscopic retrograde cholangiopancreatography, cannulation success

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Conflict of Interest: None

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) represents the cornerstone modality in the management of pancreato-biliary diseases. The first step towards achieving the necessary therapeutic manipulations is to successfully cannulate the indicated duct, which can be challenging even in experienced and qualified hands [1]. Considering the common bile duct (CBD), the endoscopist can manage difficult cannulation in only 5-15% of cases, thus warranting alternative approaches [1,2].

The first choice to obtain access to the CBD includes the use of a conventional sphincterotome with a guidewire, advanced to the CBD under fluoroscopy. Nevertheless, this approach is not always effective, and current recommendations indicate alternative techniques. More specifically, guidelines published by various societies indicate the use of a needle-knife to unveil the CBD lumen and insert the guidewire—though, in case of involuntarily cannulation of the pancreatic duct (PD), the European guidelines suggest, primarily, the adoption of the double-wire technique [3,4]. On the other hand, it is suggested that proceeding with a transpancreatic sphincterotomy (TPS) should be reserved for specific cases (e.g., hypoplastic papilla), as limited data were available at the time the guidelines were issued [3,5-7]. Although this technique was initially described 3 decades ago [8], emerging reports about this cannulation variant have been published during the last years, thus indicating a potential role for TPS at an earlier stage. This retrospective study aimed to present the experience of a tertiary center with regard to cannulation success and safety, considering TPS as the first-choice alternative in case of accidental PD guidewire insertion. In addition, potential confounders associated with the aforementioned outcomes were also investigated.

Materials and methods

Study design

A single-center, retrospective, cohort study was conducted using the records of an internal electronic database of patients hospitalized in the Department of Gastroenterology of the General University Hospital of Larissa, following the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines (Supplementary Table 1). This academic tertiary hospital provides medical services in a region with approximately 1 million citizens and represents a high-volume center for ERCP, with about 1000 procedures annually [9]. Eighty-eight datasets from a 5-year period were retrieved, from September 2015 to August 2020.

The study protocol conformed to the ethical guidelines of the last revision of the Declaration of Helsinki and complied with Good Clinical Practice Guidelines [10,11]. The study was approved by the regional research committee and patients' anonymity was ensured.

Data collection

All patients undergoing ERCP for first time were eligible to participate in the study. Exclusion criteria comprised: a) previous history of ERCP; b) history of surgeries changing the normal anatomy of interest (e.g., Billroth II, Roux-en-Y or biliary-intestinal anastomosis); c) ERCP combined with percutaneous transhepatic cholangiography or surgery by the rendezvous technique; and d) missing or incomplete data in the electronic database.

Cases fulfilling the eligibility criteria during the aforementioned period were recruited. The eligibility of the included cases was evaluated by AP. Patients' records were retrieved by TF, CK, KP and FF, from AKTIS (v.1.6.8 for Windows, Aktis Computers Software®, Greece), a clinical application that enables the storage and retrieval of multiple medical reports, including history, clinical findings, laboratory and imaging examinations, endoscopic procedures and outcome information of all patients admitted. The following variables were evaluated: 1) sex; 2) age; 3) indication to perform ERCP; 4) the presence of periampullary diverticulum; 5) the papilla endoscopic classification (Type 1, regular papilla; Type 2, small papilla, flat, with a diameter ≤3 mm; and Type 3, protruding or pendulous papilla); 6) the necessity for precut technique application; 7) the necessity for TPS; 8) the final outcome of cannulation during the first ERCP, defined as success or failure; and 9) the occurrence of adverse events, namely post-ERCP pancreatitis (PEP), bleeding or perforation.

An Excel file (Microsoft® Excel for Mac 2019, Microsoft Corporation, Redmond, WA, USA) was created and the variable values were extracted. All data were stored on a secure server. In cases of conflict, a consensus was achieved via the intervention of a senior author (AP).

Procedures

Baseline values for biochemical liver function tests, amylase, electrolytes, complete blood count and coagulation metrics were routinely determined for all patients before the procedure. In addition, our department conforms with European Society of Gastrointestinal Endoscopy (ESGE) guidelines regarding the standard of care measures to reduce the risk of complications. In this regard, all patients with naïve papilla received supp. diclofenac 100 mg, around 30 min before ERCP, and were hydrated with intravenous fluids, mainly using Ringer's lactated solution, based on their renal and cardiac functional status. To prevent post-sphincterotomy hemorrhage, platelet count and prothrombin time were assessed and patients antiplatelet/anticoagulant medications were modified based on existing recommendations.

Briefly, ERCP was performed using a side-viewing therapeutic duodenoscope, with patients under sedation with midazolam, and occasionally fentanyl, administered by a physician-assistant, who also monitored oxygen saturation and heart rate during the procedure. CBD cannulation was initially attempted using a conventional sphincterotome, assisted by a single hydrophilic guidewire. The definition of difficult cannulation followed the ESGE terminology of the 5-5-2 rule. The vast majority of procedures were attempted by a fellow under supervision; when the cannulation was

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difficult, the procedure was continued by an experienced endoscopist (AnK or SP), who performed more than 400 ERCPs annually.

When TPS was necessary, the guidewire was left in the PD and the sphincterotome was directed to the CBD to abolish the septum between PD and CBD, using the ENDO-CUT mode of the electrosurgical unit (Erbe Elektromedizin GmbH, Germany). After completion of TPS, a pancreatic pigtail stent was inserted into the PD, to avoid intraductal migration, and CBD cannulation was subsequently attempted; in some cases extension of the incision was performed using a needle-knife. Fig. 1 illustrates the TPS steps for guidewire insertion into the PD.

After ERCP, all patients were monitored for at least 24 h to diagnose any potential complications. If a pancreatic stent had been placed, it was removed 48 h later.

Outcomes and definitions

The primary outcome was successful cannulation after TPS, defined as one-session deep guidewire insertion into the CBD. The secondary outcomes included the safety of this modality, especially considering PEP, diagnosed when abdominal pain attributable to acute pancreatitis was presented, together with a need for further hospitalization, and serum amylase at least 3 times above the upper limit of normal at 18-24 h after the procedure [12,13]. Post-procedural bleeding included cases requiring hemostasis immediately after sphincterotomy or during the next 15 days, and perforation after imaging documentation. Finally, potential variables affecting the need for TPS and the success or complication rates of this modality were investigated to outline the optimal conditions for this technique.

Statistical analysis

Data were presented as mean ± standard deviation (SD) and percentages, for continuous and categorical variables, respectively. The comparisons of continuous and categorical variables were performed with the Mann-Whitney test and chi-square (χ^2) test (or the Fisher's exact test), respectively. The normality of distribution of continuous variables was tested with the Kolmogorov-Smirnov test, and the Mann-Whitney test was used for comparisons between groups. Binary logistic regression analysis was performed to investigate whether the outcome of cannulation was independently associated with the independent variables. Additionally, a further multivariate logistic regression analysis was performed to investigate the relation of ampullary anatomy and ERCP indication to precut technique and TPS incidence. Statistical analysis was performed using SPSS 21.0 for Macintosh (IBM Corp., Armonk, NY, USA). Significance was set at 2-tailed $P<0.05$.

Results

After removal of duplicates, 2685 records were retrieved and 1082 individual patients were finally eligible for analysis. Table 1 summarizes the main characteristics of our sample. Almost equal distribution between sexes was recorded (47.7% female) and the mean age was 72.7 (±15.82) years. The vast majority of patients (81.9%) presented with a benign condition as indication for ERCP. More specifically, cholangitis or biliary pancreatitis was diagnosed in 363 (33.4%) of cases, and 503 had CBD stones in imaging, without active inflammation. Neoplastic diseases indicating ERCP consisted of cholangiocarcinoma and pancreatic

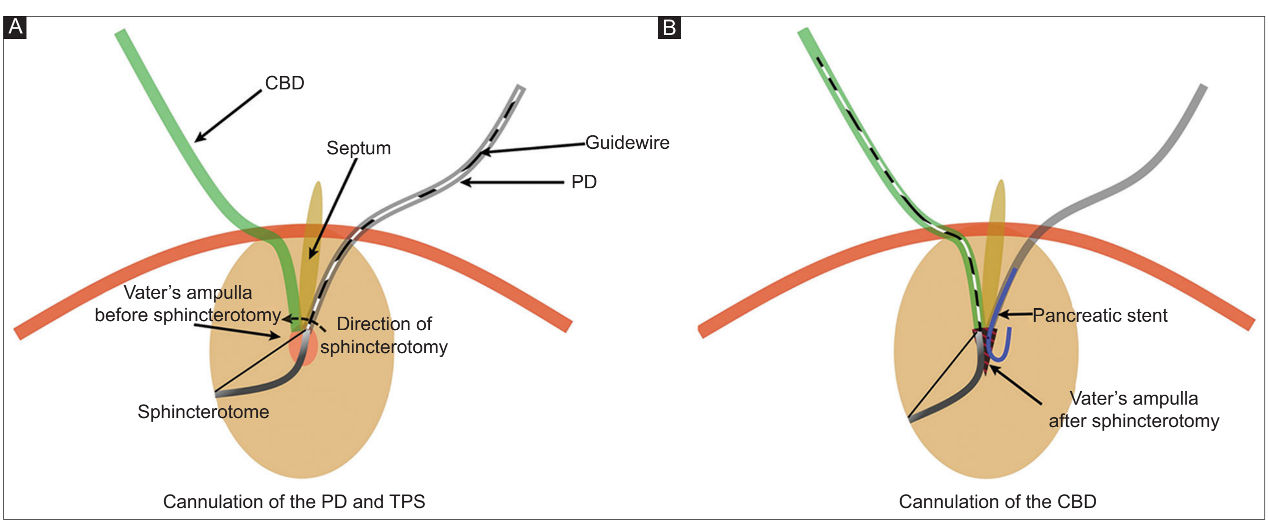

Figure 1 Illustration of the TPS technique. (A) After PD cannulation a sphincterotomy is performed in the direction of the CBD (10^{th}-11^{th} endoscopic h) until incision of the septum. The next step (B) includes the insertion of a pancreatic stent in the PD and deep cannulation of the revealed CBD. When needed, additional sphincterotomy can be performed to facilitate therapeutic manipulations
CBD, common bile duct; PD, pancreatic duct; TPS, transpancreatic sphincterotomy

cancer in 16.2% of patients, while 21 patients with bile outflow obstruction due to ampullary tumors were detected. Periampullary diverticulum was detected in 156 (14.4%) cases and the morphology of the ampulla was normal in 739 (68.0%), hypoplastic in 45 (4.1%) and protruding in 300 (27.6%) of cases.

Conventional cannulation technique was effective in 958 (88.5%) cases, before further techniques were attempted. Among the cases with primary failure, 73 (58.9%) underwent TPS, with a success rate of 95.9%, thus increasing the overall cannulation yield to 94.8%. The overall percentage of complications rose to 10.4%, with PEP occurring in 22 cases (2%), bleeding in 43 (3.97%), and perforation in 5 patients (0.46%). Interestingly, the incidence of adverse events after TPS rose to 16.7% (P=0.008) compared to the overall complication rate, though the incidence of PEP remained low (2.8%, P=0.53). Contrariwise, post-ERCP hemorrhage was diagnosed in 8 patients after TPS (10.9%, P=0.005).

With regard to potential predispositions to attempt TPS, periampullary diverticulum (P=0.33) and Vater's ampulla morphology (P=0.342) did not affect the selection of alternative method. Nevertheless, cases with malignant CBD obstruction underwent TPS more commonly after conventional technique failure (P=0.002) and 17 patients (23.3%) had previously undergone a precut fistulotomy attempt.

Multivariate regression analysis assessed the risk factors for post-ERCP complications, and PEP was associated with previous precut attempts (risk ratio [RR] 3.104, 95% confidence interval [CI] 1.03-9.36; P=0.04), whereas TPS was negatively associated with PEP (RR 0.015, 95%CI 0.23-5.05; P<0.001). Similarly, bleeding was increased after needle-knife application (RR 3.02, 95%CI 1.42-6.43; P=0.004) and TPS preserved a negative linkage (RR 0.03, 95%CI 1.01-5.63; P<0.001). Table 2 illustrates the results of the regression analysis.

Table 1 Main characteristics of included sample

Variable	n (%)
Female sex	516 (47.7)
Age, mean (SD), years	72.7 (±15.82)
Indication	
Lithiasis	503 (46.5)
Cholangitis/pancreatitis	363 (33.4)
CCC/PC	176 (16.2)
Ampullary neoplasm	21 (1.9)
Surgical complication	19 (1.8)
Diverticulum (yes)	156 (14.4)
Papilla morphology	
Normal	739 (68.0)
Hypoplastic	45 (4.1)
Protruding	300 (27.6)
Success with conventional technique	958 (88.5)
TPS	73 (58.9)
Success with TPS	70 (95.9)
Complications (overall)	
PEP	22 (2.0)
Cholangitis/cholecystitis	43 (3.97)
Bleeding	43 (3.97)
Perforation	5 (0.46)
Complications (after TPS)	
PEP	2 (2.8)
Cholangitis/cholecystitis	2 (2.8)
Bleeding	8 (10.9)
Perforation	0 (0.0)

CCC, cholangiocarcinoma; PC, pancreatic cancer; PEP, post-endoscopic retrograde cholangiopancreatography pancreatitis; SD, standard deviation; TPS, transpancreatic sphincterotomy

Discussion

This study aimed to redetermine the role of TPS in CBD cannulation at an early stage, after initial failure, with regard to success and safety. The application of TPS increased the success rate of CBD access by 6.3%, thus increasing the overall cannulation rate during ERCP to 94.8%, for conventional and TPS techniques. Those results are in compliance with recent data showing that TPS could facilitate CBD access more effectively than the standard double-wire technique. More specifically, Kylänpää *et al* [14], in a randomized controlled trial, concluded that TPS was significantly more effective than the double-wire technique in achieving CBD cannulation (84.6% vs. 69.7%; P=0.01), with no additional impact on PEP. Cumulative comparisons among all available techniques, presented in a recent network meta-analysis, indicated the superiority of TPS over the other alternatives (RR vs. standard

Table 2 Regression analysis of post-TPS complications

Variables	PEP				Bleeding			
	Exp (B)	P-value	95%CI		Exp (B)	P-value	95%CI	
			Lower	Upper			Lower	Upper
Female sex	0.953	0.916	0.390	2.331	0.846	0.602	0.452	1.584
Needle-knife use	3.104	0.044	1.029	9.363	3.024	0.004	1.423	6.426
TPS	0.015	<0.001	0.231	5.051	0.031	<0.001	1.010	5.633
Malignancy	1.195	0.742	0.413	3.463	1.506	0.252	0.747	3.033

CI, confidence interval; PEP, post-ERCP pancreatitis; TPS, transpancreatic sphincterotomy sphincterotome: 1.29, 95%CI 1.05-1.59; RR vs. double wire technique: 1.21, 95%CI 1.01-1.44); RR vs. needle-knife: 1.19, 95%CI 1.01-1.43); RR vs. pancreatic stent-assisted technique: 1.47, 95%CI 1.03-2.10), whereas only precut papillotomy was also superior to the standard sphincterotome approach [15]. Moreover, TPS has been considered to have a shorter learning curve compared with the needle-knife technique, though additional evidence is required to establish an official suggestion in the training curriculum [16,17].

Additionally, the safety of the procedure was evaluated in our cohort in terms of the most common adverse events. The overall complication rate was significantly greater after TPS (16.7%, P=0.008), largely because of the subgroup of post-ERCP bleeding (10.9%, P=0.005). Initial reports implicated the incision of an aberrant retroduodenal artery during TPS [8,18]. Nevertheless, in our study, these results probably represent an artifact, due to the overlap with needle-knife incision. This is mainly supported by the regression analysis, which indicated that the only factor positively associated with post-ERCP bleeding, was the attempt to perform fistulotomy (RR 3.02, 95%CI 1.42-6.43; P=0.004), whereas TPS reduced this risk (RR 0.03, 95%CI 1.01-5.63; P<0.001). This could be explained by 2 potential mechanisms. The first, corresponding to the increased post-fistulotomy bleeding ratio, reflects the predisposition to unstable cutting using the "free-hand" needle-knife technique, whereas the lower hemorrhage prevalence in the TPS group could be influenced by the stable intraductal position of the sphincterotome, as well as by the potential tamponade effect of the pancreatic stent.

The strategy of inserting a pancreatic stent after TPS has already been considered crucial for the reduction of PEP. Our results demonstrated that TPS was negatively associated with PEP (2.8% of cases; RR 0.015, 95%CI 0.23-5.05; P<0.001), thus indirectly indicating the protective effect of a pancreatic stent. Similarly, Facciorusso *et al* [15] demonstrated that TPS provided lower rates of PEP compared to the double-wire technique (RR 0.49, 95%CI 0.23-0.99). Contrariwise, in our analysis precut sphincterotomy was a risk factor for PEP (RR 3.104, 95%CI 1.03-9.36; P=0.04), whilst in the abovementioned review the authors reported a lower incidence of PEP using this technique compared to the double-wire assistance (RR 0.53, 95%CI 0.30-0.92). In this regard, TPS could be considered earlier in cases of difficult cannulation, and in some cases before precut application.

Finally, some hypotheses exist regarding the long-term impact of TPS on chronic pancreatitis and the incidence of benign strictures [19]. To our knowledge, none of the included patients were readmitted with such manifestations, though the retrospective design of our analysis did not provide data regarding TPS follow up. Moreover, the predominance of malignant obstruction as indication for TPS in the vast majority of those patients did not allow safe conclusions to be drawn about the causes of potential obstruction recurrences.

To date, 2 conditions have been recognized as potential predictors of TPS: unintentional PD cannulation; and small papilla [3]. Concerning the ampulla morphology, our reports categorized its macroscopic appearance into 3 groups, whilst none of them was associated with the decision to proceed to TPS. Although the retrospective design of our study did not allow the assessment of homogeneity in the interpretation of papilla anatomy, a consensus with the supervisor endoscopists (AnK and SP) confirmed a basic, although arbitrary, interobserver agreement and the absence of its impact on the decision to perform TPS. Similarly, the presence of a periampullary diverticulum neither impeded the selection of TPS nor affected the complication rates. On the other hand, when malignant CBD obstruction was the indication for ERCP, TPS was more commonly applied (P=0.001). This probably reflects the rate of unintentional wire insertion into the PD, due to its dilatation, at least in some cases. Although PD diameter has not been implicated in inadvertent PD cannulation, the combination of CBD obstruction and PD dilation represents a rational condition for PD guidewire insertion. Tumors located in the papilla, the pancreatic head or the distal CBD can create a concomitant dilation in both ducts, illustrated as the "double-duct" sign in preprocedural imaging [20,21]. This could be used as a guide to decide on early TPS in case of difficult cannulation, though further studies are needed to validate this approach.

Despite the emerging advantages of TPS in terms of cannulation success, combined with the low rates of adverse events, there are some significant obstacles, which need consideration before the existing algorithms can be modified. Although the theoretical definition of TPS includes the abolition of the septum between ducts, the practical landmarks to confirm its completion remain unclear. Depending on the endoscopist, the endpoint of TPS has been defined as the exposure of the CBD, the clear division of CBD and PD orifices, or the complete incision of Oddi's sphincter [22,23]. Moreover, in some cases, complementary cutting with a needle-knife could be applied over the pancreatic stent in the direction of the CBD (10^{th}-11^{th} endoscopic h) [23] In our institution, a more conservative approach has been adopted, including an initial incision of 3-4 mm, insertion of a pancreatic stent, deep cannulation of the CBD and a complementary sphincterotomy of the remaining sphincter. Those techniques require an advanced level of experience, whilst there are no established measures to guide training. The current curriculum in ERCP, based on the Schutz classification, does not suggest any performance standards before attempting TPS, although it could be hypothesized that it should be reserved for endoscopists competent in ERCP [24,25]. Nevertheless, the learning curve and the minimum procedures to qualify for TPS require further assessment by future studies, as no relevant publications exist [26].

This study also had some limitations. First, its retrospective design cannot ensure the homogeneity of procedures and the comparison with alternative techniques. Furthermore, the vast majority of cannulation efforts were initially attempted by trainees, given the academic orientation of our department. Thirdly, although our general strategy in the cannulation process is based on ESGE guidelines, it could not be definitively confirmed that the 5-5-2 rule was absolutely applied in all procedures, as in some cases the senior endoscopist might have made some more attempts, depending on a case-based approach. Finally, cases without complications during the first

24 h were discharged, and potential readmissions due to late adverse events or incomplete drainage could have been missed.

In conclusion, TPS, combined with pancreatic stenting, comprises an effective and safe choice in cases with difficult CBD cannulation when performed in high-volume centers, thus increasing the success rates to 95%. Moreover, the prevalence of common post-ERCP complications does not increase, probably because of the protective impact of PD stents. A careful preprocedural assessment is necessary to guide the decision making in case of difficult cannulation, as the indication seems to be a significant factor affecting TPS, when it concerns malignancy.

Summary Box

What is already known:

- Transpancreatic sphincterotomy (TPS) can increase the success rate of common bile duct (CBD) cannulation in difficult cases of endoscopic retrograde cholangiopancreatography (ERCP)
- Pancreatic stenting prevents post-ERCP pancreatitis
- TPS should be performed by experienced endoscopists

What the new findings are:

- TPS could be the initial alternative after conventional technique failure in cases with malignant CBD obstruction
- TPS with pancreatic stenting could reduce the rate of post-ERCP bleeding using a needle-knife
- The optimal balance between success and complication rates could guide future algorithm revision in favor of TPS

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Supplementary material

Supplementary Table 1 Strengthening the reporting of observational studies in epidemiology (STROBE) statement

	Item No	Recommendation	Pages in the manuscript
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow up	5
		(b) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7,8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7,8
		(b) Describe any methods used to examine subgroups and interactions	7,8
		(c) Explain how missing data were addressed	
		(d) If applicable, explain how loss to follow up was addressed	
		(e) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders	8, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarize follow-up time (e.g., average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8 8,9
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	8,9
Discussion			
Key results	18	Summarize key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-11
Generalisability	21	Discuss the generalizability (external validity) of the study results	12
Other information Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1