Development of upper gastrointestinal cancer in patients with symptomatic gallstones, cholecystectomy, and sphincterotomy: A nationwide cohort study

Daniel M. Shabanzadeh, Torben Martinussen and Lars T. Sørensen

Abstract

Background and objective: Exposures of gallstones and treatments thereof in relation to development of cancer have not been explored before in long-term follow-up studies. Our objective was to determine whether symptomatic gallstones, cholecystectomy, or sphincterotomy were associated with development of upper gastrointestinal cancers.

Methods: This is a nationwide cohort study of persons born in Denmark 1930–1984 included from age 30 years with long-term follow-up (1977–2014). Exposures were hospital admissions with gallstones, cholecystectomy, and sphincterotomy. Time-varying covariates were included in analyses to allow the impact of exposures to change with time. Follow-up periods were 2–5 and >5 years. Hazard ratios (HR) with 95% confidence intervals (CI) were reported.

Results: A total of 4,465,962 persons were followed. We found positive associations between sphincterotomy and biliary (>5 years HR 4.34, CI [2.17–8.70]), gallbladder (2–5 years HR 20.7, CI [8.55–50.1]), and pancreatic cancer (2–5 years HR 3.68, CI [2.09–6.49]). Cholecystectomy was positively associated with duodenal (2–5 years HR 2.94, CI [1.31–6.58]) and small bowel cancer (2–5 years HR 2.75, CI [1.56–4.87]). Inverse associations were seen for cholecystectomy and biliary (>5 years HR 0.60, CI [0.41–0.87]), pancreatic (>5 years HR 0.45 CI [0.35–0.57]), esophageal (>5 years HR 0.57, CI [0.43–0.74]), and gastric cancer (>5 years HR 0.68, CI [0.55–0.86]) and for gallstones and pancreatic cancer (>5 years HR 0.66, CI [0.47–0.93]). Gallstones were positively associated with gallbladder (>5 years HR 3.51, CI [2.02–6.10]) and small bowel cancer (2–5 years HR 3.21, CI [1.60–6.45]).

Conclusions: A positive association between sphincterotomy and biliary cancer was identified. Cholecystectomy seems to be inversely associated with biliary, pancreatic, esophageal, and gastric cancer. Associations should be explored in similar large cohorts.

Keywords

Cholangiopancreatography, endoscopic retrograde, cholelithiasis, epidemiology, ERCP, follow-up studies

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Context and Relevance

Specific exposures of gallstones, cholecystectomy, and sphincterotomy in relation to development of upper gastrointestinal cancer have not been explored before in long-term follow-up studies. In this nationwide cohort study including persons born in Denmark 1930–1984, we find a positive association between sphincterotomy and biliary cancer after more than 5 years of follow-up. Cholecystectomy seems to be inversely associated with biliary, pancreatic, esophageal, and gastric cancer.

Introduction

Gallstones and possible derived treatments have shown to be associated with occurrence of several gastrointestinal cancers.1,2 Previous smaller clinical studies have suggested associations for cancer and sphincterotomy3–5 and larger cohorts also for cholecystectomy,2 but have been unable to explore whether it is the presence of gallstones or their treatments that cause development of gastrointestinal cancers. This may be due to unavailability of lifelong follow-up data, not exploring the impact of sphincterotomy, and for not including the changing exposures for gallstones and treatments in time-to-event analyses with long-term follow-up. There is a need for exploring potential harmful effects of specific gallstone treatments.

Gallstones are highly prevalent in general populations and their associated clinical conditions lead them to be among the most frequent gastrointestinal diagnoses for hospital admissions causing high health care costs and burden.6,7 Standard treatment for symptomatic gallstones is cholecystectomy.8 Laparoscopic cholecystectomy is the most frequent surgical procedure of the gastrointestinal system in Scandinavian countries, and frequencies are on the rise in other European countries.9,10 Endoscopic retrograde cholangiography (ERC) is performed when common bile duct stones are suspected with the aim of performing therapeutic sphincterotomy and stone extraction.8 ERC rates have been rapidly increasing within the recent decade in North America.11,12

The sequence of clinical events in persons with gallstones may include a period from diagnosis of symptomatic gallstones to the performance of surgical treatments, which may be years apart. This causes a long period with changing exposures of gallstones, sphincterotomy, and cholecystectomy. All hospital contacts for Danish residents are registered centrally with diagnose and intervention codes, enabling long-term and complete follow-up.13 Thereby, the full impact of gallstones, sphincterotomy, cholecystectomy, and the changing exposures throughout a lifetime on incidence of gastrointestinal cancers may be explored.

The objective was to determine whether hospital admissions with gallstones, cholecystectomy, or sphincterotomy were associated with development of site-specific upper gastrointestinal cancer divided into biliary, gallbladder, hepatic, pancreatic, esophageal, gastric, duodenal, and small bowel cancer in a nationwide population cohort with long-term follow-up.

Methods

This is a nationwide cohort study including all persons born in Denmark in the years 1930–1984. Persons were included when turning 30 years of age as this was considered relevant for gallstone formation and for established socioeconomic conditions. Persons were followed until occurrence of upper gastrointestinal cancer, death, hepatic metastasis, or were censored if moving out of the country, whichever came first. Hepatic metastasis may be the debuting sign of disseminated gastrointestinal cancer without a site-specific cancer of origin ever being identified, and therefore these cases were censored if occurring before a site-specific gastrointestinal cancer. Persons were excluded if the explored cancers or liver metastasis had occurred before the age of 30 years. A varying number of persons may therefore have been included at baseline in analyses of site-specific cancer outcomes. When exploring gallbladder cancer, we censored patients that had cholecystectomy performed.

Persons were follow-up through Danish national registers. The Danish Central Person Registry contains daily updated information on vital status and migration of the entire nation. A unique personal registration number enables linkage to other registers.13 The National Patient Registry contains data on all hospital admissions from the year 1977 and emergency room visits from 1995. It includes diagnose codes according to the International Classification of Disease (ICD 8 or ICD 10—ICD 9 was never used in Denmark) and surgical intervention codes according to the Nordic Classification of Surgical Procedures. Codes are registered at the time of discharge from the hospital.14 The Danish Register of Causes of Death contains one underlying cause of death with up to three contributory causes according to the ICD since 1970.15 The National Patient Registry and The Danish Register of Causes of Death were used for identification of cancer outcome diagnoses, and The National Patient Registry was used to assess gallstone and treatment exposures. Statistics Denmark was used to obtain data on socioeconomic conditions. The National Patient Registry was updated at the end of 2014, The Danish Register of Causes of Death at the end of 2015, and The Danish Central Person Registry and Statistics Denmark in 2016. All registers have been used frequently in epidemiological research.13–15

The outcome of interest was site-specific upper gastrointestinal cancer divided into biliary, gallbladder, hepatic, pancreatic, esophageal, gastric, duodenal, and small bowel cancer. Exposure variables included cholecystectomy, sphincterotomy, presence of both interventions performed, or gallstones without interventions performed. For detailed definitions of exposures and outcomes see Table 1.
Socioeconomic variables were included as covariates in multivariable models and served as proxy for lifestyle and anthropometric data, as both gallstones and gastrointestinal cancer may be associated with these. Socioeconomic variables were assessed once when the person was 30 years of age where possible. Covariates included sex (female/male), socioeconomic status (employee, self-employed/manager, retired, student, temporary transfer income/on leave, transfer income/unemployed), civil status (married/registered partner, unmarried, widowed, divorced), level of education (high school/elementary school, vocational training, short/medium-term education, higher university education), and personal annual income (DKK). Primary sclerosing cholangitis is highly associated with biliary cancer when compared with the risk in the general population. Sensitivity analyses were, therefore, performed to explore the possible confounding pathway for primary sclerosing cholangitis, sphincterotomy, and biliary cancer. The study was reported according to the STROBE statement.

Ethical approval for performing the study was given through the Danish Data Protection Agency and the Capital Region of Denmark (journal number CSU-FCFS-2017-007, I-Suite number 05575). As no new human data were collected, no participants provided informed consent was required.

**Statistical analyses**

Competing risk analyses were used with age as the underlying timescale. Death was used as the competing cause when analyzing the occurrences of the site-specific cancer outcomes. We modeled the cause-specific hazard functions using the Cox proportional hazards model with time-varying covariates to allow the impact of the different exposures to change with time. Time periods of 0–2 years, 2–5 years, and more than 5 years since exposure was used. Unexposed persons served as the controls. Based on the cause-specific hazard models, we computed cumulative incidence functions to quantify exposure effects on the probability scale. We did not report results from the period of 0–2 years since exposure to avoid prevalent cancers. We report number of outcome cases, total persons in exposure category, person years, incidence rate as cases per 100,000 person years, crude cumulative incidence curves, and hazard ratios (HR) with 95% confidence intervals (CI) both unadjusted and adjusted for baseline covariates. Significance level is set as a 95% CI not including one. Statistical software R with the “survival” package was used for analyses.

**Results**

The nationwide cohort included 4,465,962 persons in the period 1977–2014. For baseline characteristics, see Table 2. During follow-up, the most frequently occurring cancers were pancreatic, gastric, and esophageal. The rarest occurring cancers were duodenal, gallbladder, and small bowel. Hepatic and biliary cancers occurred with frequencies in between (Table 3).
When inspecting the crude cumulative incidence curves, patients with gallstones have higher incidence of biliary and gallbladder cancer than controls, whereas patients after sphincterotomy have much higher incidence of biliary, gallbladder, hepatic, and pancreatic cancer. Patients with both cholecystectomy and sphincterotomy have higher incidence of biliary and pancreatic cancers.

Patients with cholecystectomy have lower incidence of pancreatic and gastric cancer than controls (Fig. 1).

Estimates for unadjusted and adjusted analyses were very similar regarding significance level in both exposure periods, except for gastric cancer (Table 3).

Patients with gallstones significantly more often developed biliary and small bowel cancer at 2–5 years of follow-up and gallbladder cancer at above 5 years compared with controls. Those with cholecystectomy had higher incidence of biliary and pancreatic cancers. Patients with cholecystectomy and sphincterotomy have higher incidence of biliary, hepatic, and pancreatic cancer. Patients with both cholecystectomy and sphincterotomy also had higher incidence of biliary and pancreatic cancers.

Table 3. Gallstones and treatments thereof in relation to development of upper gastrointestinal cancers.

| Cancer | Exposure | Cases | Person years | Total | Incidence rate<sup>a</sup> | Unadjusted HR [95% confidence interval] | Adjusted<sup>b</sup> HR [95% confidence interval] |
|--------|----------|-------|--------------|-------|---------------------------|----------------------------------------|-----------------------------------------------|
|        |          |       |              |       |                           | 2–5 y | >5 y |          | 2–5 y | >5 y |          | 2–5 y | >5 y |          | 2–5 y | >5 y |          |
|        |          |       |              |       |                           |       |      |          |       |      |          |       |      |          |       |      |          |
| Biliary | Unexposed | 3704 | 101,732,394 | 4,442,772 | 3.64 | 2.47 [1.49-4.10] | 1.27 [0.82-1.95] | 1.96 [1.09-3.55] | 1.04 [0.64-1.71] |
|        |          |       |              |       |                           |       |      |          |       |      |          |       |      |          |       |      |          |
|        | Gallstones | 253  | 635,631    | 146,068 | 39.8 | 1.27 [0.82-1.95] | 1.96 [1.09-3.55] | 1.04 [0.64-1.71] |
|        | Cholecystectomy | 115 | 1,623,118 | 129,265 | 7.09 | 0.99 [0.55-1.78] | 0.58 [0.40-0.84] | 0.88 [0.46-1.69] | 0.60 [0.41-0.87] |
|        | Sphincterotomy | 391 | 75,652    | 22,080   | 516.8 | 11.2 [6.34-19.7] | 4.12 [2.04-8.26] | 10.6 [5.84-19.1] | 4.34 [2.17-8.70] |
|        | Cholecystectomy and sphincterotomy | 48 | 157,960 | 17,091 | 30.4 | 2.98 [1.24-7.15] | 1.20 [0.50-2.89] | 3.21 [1.33-7.71] | 1.31 [0.55-3.16] |
| Galbladder | Unexposed | 769 | 101,758,422 | 4,442,959 | 0.76 | 3.76 [1.56-9.08] | 3.76 [2.21-6.40] | 3.69 [1.61-9.40] | 3.51 [2.02-6.10] |
|        | Gallstones | 95   | 636,909    | 146,310 | 14.9 | 3.76 [1.56-9.08] | 3.76 [2.21-6.40] | 3.69 [1.61-9.40] | 3.51 [2.02-6.10] |
|        | Sphincterotomy | 55  | 77,089   | 22,744   | 71.3 | 20.2 [8.35-48.8] | 2.21 [0.31-15.7] | 20.7 [8.55-50.1] | 2.29 [0.32-16.3] |
| Hepatic  | Unexposed | 5063 | 101,705,574 | 4,442,590 | 4.98 | 2.14 [0.84-5.26] | 1.09 [0.74-1.60] | 1.54 [0.87-2.71] | 1.07 [0.71-1.63] |
|        | Gallstones | 136 | 635,407    | 146,120 | 4.98 | 1.45 [0.84-2.50] | 1.09 [0.74-1.60] | 1.54 [0.87-2.71] | 1.07 [0.71-1.63] |
|        | Cholecystectomy | 94 | 1,623,158 | 129,388 | 4.57 | 0.64 [0.36-1.16] | 0.63 [0.47-0.85] | 0.67 [0.35-1.29] | 0.76 [0.55-1.03] |
|        | Sphincterotomy | 78  | 76,742   | 22,564   | 101.6 | 1.99 [0.64-6.16] | 1.85 [0.77-4.45] | 1.98 [0.64-6.46] | 1.93 [0.80-4.65] |
|        | Cholecystectomy and sphincterotomy | 20 | 158,612 | 17,277 | 12.6 | 1.21 [0.39-3.74] | 0.50 [0.16-1.55] | 1.46 [0.47-4.54] | 0.64 [0.21-2.00] |

(Continued)
| Cancer                        | Exposure          | Cases | Person years | Total  | Incidence rate | Unadjusted HR [95% confidence interval] | Adjusted* HR [95% confidence interval] |
|------------------------------|-------------------|-------|--------------|--------|----------------|----------------------------------------|----------------------------------------|
|                              |                   |       |              |        |                | 2–5 y | >5 y         | 2–5 y | >5 y          |
| Pancreatic                   | Unexposed         | 13,511| 101,593,121  | 4,442,070 | 13.3           | Ref. | Ref.         | Ref. | Ref.         |
| Gallstones                   |                   | 264   | 63,412       | 145,446 | 4.16           | 0.82 [0.52–1.30] | 0.63 [0.46–0.88] | 0.90 [0.57–1.43] | 0.66 [0.47–0.93] |
| Cholecystectomy              |                   | 153   | 1,618,051    | 128,555 | 9.46           | 0.32 [0.19–0.54] | 0.44 [0.35–0.55] | 0.27 [0.15–0.50] | 0.45 [0.35–0.57] |
| Sphincterotomy               |                   | 370   | 73,854       | 20,245  | 501.0          | 3.85 [2.23–6.63] | 0.67 [0.25–1.78] | 3.68 [2.09–6.49] | 0.72 [0.27–1.91] |
| Cholecystectomy and sphincterotomy |               | 55    | 157,619      | 16,884  | 34.9           | 1.00 [0.45–2.22] | 0.50 [0.24–1.04] | 1.11 [0.50–2.46] | 0.49 [0.22–1.08] |
| Esophageal                   | Unexposed         | 8981  | 101,670,345  | 4,442,528 | 8.83           | Ref. | Ref.         | Ref. | Ref.         |
| Gallstones                   |                   | 112   | 635,872      | 146,216 | 17.6           | 0.58 [0.31–1.08] | 0.79 [0.57–1.09] | 0.68 [0.36–1.26] | 0.93 [0.67–1.29] |
| Cholecystectomy              |                   | 82    | 1,623,628    | 129,484 | 5.05           | 0.44 [0.26–0.74] | 0.65 [0.32–0.53] | 0.50 [0.29–0.89] | 0.57 [0.43–0.74] |
| Sphincterotomy               |                   | 21    | 76,998       | 22,766  | 27.3           | 0.98 [0.32–3.04] | 0.55 [0.18–1.69] | 0.96 [0.31–2.99] | 0.57 [0.18–1.75] |
| Cholecystectomy and sphincterotomy |               | 9     | 158,668      | 17,297  | 5.67           | 0.21 [0.03–1.48] | 0.42 [0.18–1.02] | 0.25 [0.04–1.81] | 0.55 [0.23–1.33] |
| Gastric                      | Unexposed         | 10,044| 101,666,007  | 4,442,388 | 9.88           | Ref. | Ref.         | Ref. | Ref.         |
| Gallstones                   |                   | 160   | 635,251      | 146,032 | 25.2           | 1.02 [0.66–1.58] | 0.65 [0.47–0.91] | 1.14 [0.72–1.78] | 0.72 [0.52–1.02] |
| Cholecystectomy              |                   | 129   | 1,621,951    | 129,326 | 7.95           | 0.62 [0.41–0.94] | 0.54 [0.44–0.67] | 0.65 [0.41–1.04] | 0.68 [0.55–0.86] |
| Sphincterotomy               |                   | 26    | 76,902       | 22,731  | 33.8           | 0.56 [0.14–2.24] | 0.93 [0.42–2.07] | 0.56 [0.14–2.26] | 0.81 [0.34–1.96] |
| Cholecystectomy and sphincterotomy |               | 12    | 158,615      | 17,288  | 7.57           | 0.55 [0.18–1.71] | 0.37 [0.15–0.88] | 0.66 [0.21–0.84] | 0.46 [0.19–1.10] |
| Duodenal                     | Unexposed         | 649   | 101,759,604  | 4,442,962 | 0.64           | Ref. | Ref.         | Ref. | Ref.         |
| Gallstones                   |                   | 31    | 636,623      | 146,376 | 4.87           | 2.21 [0.71–6.87] | 0.25 [0.04–1.81] | 2.35 [0.76–7.33] | 0.27 [0.04–1.93] |
| Cholecystectomy              |                   | 23    | 1,624,518    | 129,542 | 1.42           | 2.72 [1.22–6.08] | 0.72 [0.36–1.45] | 2.94 [1.31–6.58] | 0.78 [0.39–1.57] |
| Sphincterotomy               |                   | 33    | 77,092       | 22,811  | 42.8           | 3.58 [0.50–25.5] | 1.92 [0.27–13.7] | 3.61 [0.51–25.7] | 1.96 [0.28–14.0] |
| Cholecystectomy and sphincterotomy |               | 9     | 158,766      | 17,308  | 5.67           | 2.62 [0.37–18.6] | 2.94 [0.95–9.17] | 2.74 [0.39–19.5] | 3.11 [0.97–9.69] |
| Small bowel                  | Unexposed         | 1,991 | 101,754,031  | 4,442,915 | 1.37           | Ref. | Ref.         | Ref. | Ref.         |
| Gallstones                   |                   | 71    | 636,413      | 146,340 | 11.2           | 2.93 [1.46–5.88] | 1.44 [0.79–2.61] | 3.21 [1.60–6.45] | 1.44 [0.77–2.69] |
| Cholecystectomy              |                   | 56    | 1,624,378    | 129,560 | 3.45           | 2.46 [1.40–4.35] | 1.03 [0.68–1.55] | 2.75 [1.56–4.87] | 1.15 [0.76–1.74] |
| Sphincterotomy               |                   | 15    | 77,102       | 22,821  | 19.5           | 0.00 [0.00–∞] | 1.10 [0.15–7.80] | 0.00 [0.00–∞] | 1.15 [0.16–8.19] |
| Cholecystectomy and sphincterotomy |               | 6     | 158,754      | 17,310  | 3.78           | 3.92 [1.26–12.2] | 0.52 [0.07–3.71] | 4.21 [1.35–13.1] | 0.57 [0.08–4.05] |

HR, hazard ratio; y, years; Ref., reference group.
Cases/100,000 person years.
Adjusted for sex (female, male), socioeconomic status (employee (ref.), self-employed/manager, retired, student, temporary transfer income/on leave, transfer income/unemployed), civil status (married/registered partner, unmarried, widowed, divorced), level of education (high school/elementary school (ref.), vocational training, short/medium-term education, higher university education), personal annual income.
Fig. 1. Cumulative incidence curves for cancer outcomes.
both gallbladder and pancreatic cancer development significantly more often at 2–5 years. Sphincterotomy caused biliary cancer development significantly more often at above 5 years. Those with both cholecystectomy and sphincterotomy had significant associations for biliary and small bowel cancer at 2–5 years. Inverse associations for cholecystectomy and biliary, pancreatic, esophageal, and gastric cancer at above 5 years were found (Table 3).

Sensitivity analysis for biliary cancer with addition of primary sclerosing cholangitis to the multivariable adjusted model did not change estimates substantially (Supplemental Material).

Discussion

Through long-term follow-up of a nationwide population sample and with time-varying exposures for symptomatic gallstones and treatments thereof, we found associations for sphincterotomy and biliary, gallbladder, and pancreatic cancer. Cholecystectomy was associated with duodenal and small bowel cancer. Gallstones were associated with gallbladder and small bowel cancer. Inverse associations were found for cholecystectomy and biliary, pancreatic, esophageal, and gastric cancer and for gallstones and pancreatic cancer.

We define strong and precise associations as statistically significant estimates with narrow confidence intervals and as being present after 5 years of follow-up. Such associations were identified for sphincterotomy and biliary cancer, for gallstones and gallbladder cancer, and the inverse association for cholecystectomy and pancreatic cancer. The association for sphincterotomy and biliary cancer was not altered with the inclusion of primary sclerosing cholangitis in the multivariable model indicating no issues with confounding. Both gallstones and cholecystectomy were associated with small bowel cancer. Associations did not persist beyond 5 years of exposure and it may therefore be difficult to interpret whether gallstones or cholecystectomy caused cancer development.

Another study based on the National Health Insurance Research Database in Taiwan suggested associations for sphincterotomy or sphincter of Oddi balloon dilatation and biliary cancer and also the inverse association for cholecystectomy and pancreatic cancer. The association for sphincterotomy and biliary cancer was not altered with the inclusion of primary sclerosing cholangitis in the multivariable model indicating no issues with confounding. Both gallstones and cholecystectomy were associated with small bowel cancer. Associations did not persist beyond 5 years of exposure and it may therefore be difficult to interpret whether gallstones or cholecystectomy caused cancer development.

The strength of this study is that it is the first cohort study to explore associations for specific and changing exposures of gallstones, treatments thereof, and cancer outcome in the general population. The comprehensiveness of the databases used in this study enabled all exposure treatments and occurrences of cancer to be registered nationwide without loss. The study population was also the largest reported in cohort studies exploring gallstones, treatments thereof, and cancer at the time of publication. Symptoms from a cancer may be clinically misinterpreted as gallstones as suggested earlier. To avoid such diagnostic mimicry and risk of detection bias
and to secure temporal associations, we did not include estimates during the first 2 years of follow-up. Limitations of this study include that only symptomatic gallstones causing hospital admission were identified. We know from a previous cohort study of screen-detected gallstones found in a population with systematic ultrasound screening, that clinically identified gallstones leading to hospital admission are only accountable for about one-fifth of persons with gallstones. Furthermore, specific characteristics determine symptomatic gallstones. The true gallstone prevalence is therefore underestimated in this study with risk of potential differential misclassification bias. This could cause both significant and nonsignificant estimates when the gallstone exposure was explored, and these results should therefore be interpreted with caution. Estimates for sphincterotomy and cholecystectomy do not have such risk. Anthropometric data were not available which could cause residual confounding, but we included socioeconomic variables as proxy in models to minimize the impact of such potential bias. Due to differences in initiation dates of the registries used in this study, persons may have been older than 30 years when included. This baseline difference was addressed through having age as the underlying timescale.

The strong and precise association for sphincterotomy and biliary cancer found in this large nationwide population-based cohort with long-term and advanced follow-up analyses suggest a causal association. The association’s consistency should be explored in future cohort studies including similarly large populations and design. ERC with sphincterotomy is presently the most utilized treatment for common bile duct stones. Alternatives for therapeutic common bile duct stone extraction without the use of sphincterotomy are available and have comparable clinical outcomes. For now, caution with performance of sphincterotomy is advised and especially in younger patients.

In conclusion, this large nationwide population-based cohort study identified a novel association for endoscopic sphincterotomy and development of biliary cancer after more than 5 years of follow-up. Caution with use of sphincterotomy in younger patients may be advised until further studies are performed. Cholecystectomy seems to be inversely associated with biliary, pancreatic, esophageal, and gastric cancer. These associations should be explored in larger cohort studies with similar designs in the future.

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Author contributions

D.M.S. contributed to the study design, performing analyses, interpretation of results, drafting, and final acceptance of manuscript. T.M. contributed to performing analyses, interpretation of results, critical review, and final acceptance of manuscript. L.T.S. contributed to study design, interpretation of results, critical review, and final acceptance of manuscript.

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ORCID ID

Daniel M. Shabanzadeh https://orcid.org/0000-0001-9415-3443

Supplemental material

Supplemental material for this article is available online.

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