ORIGINAL ARTICLE



Characteristics of sialolithiasis in Israel, a big-data retrospective study of 5100 cases

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Abstract

Objective: The aim of this study was to identify risk factors for sialolithiasis patients using a large community and hospital-based cohort.

Methods: A retrospective case-control study was conducted on 20,396 individuals, including 5100 sialolithiasis patients and 15,296 matched controls. Demographics and laboratory data were obtained from electronic medical records. Statistical analyses were performed to identify significant differences between the two groups. A p-value of <0.05 was considered significant.

Results: Sialolithiasis was more prevalent in women, with a mean age at diagnosis of 55.75 years. Several geographic location variables emerged as risk factors for sialolithiasis including Israeli birth, higher socioeconomic communities, and specific areas of residency. Tobacco smoking (odds ratio=1.46) was a significant risk factor. Low high-density lipoprotein levels, elevated triglycerides, and elevated amylase levels were associated with sialolithiasis.

Conclusions: This study provides valuable insights into the demographic and laboratory characteristics of sialolithiasis patients, indicating that area of residency and lifestyle factors contribute to the risk of developing sialolithiasis. The findings may contribute to a better understanding of the disease and the development of preventative measures or early diagnostics tools.

KEYWORDS

big-data, characteristics, risk factor, salivary gland stones, sialolithiasis

INTRODUCTION 1

Sialoliths are calcified deposits that form in the ducts of salivary glands, leading to a condition called sialolithiasis. This condition creates a blockage that interferes with the normal flow of saliva (Lustmann & Regev, 1990; Marchal & Dulguerov, 2003; Williams, 1999). Symptoms of sialolithiasis can differ, but often present as periodic, abrupt swelling of the afflicted gland before,

during, or after eating (often referred to as "mealtime syndrome"), along with symptoms of sialadenitis, an inflammation caused by retrograde infections from the oral cavity (Marchal & Dulguerov, 2003). Sialolithiasis comprises 30% of salivary gland pathologies and is currently thought to present in up to 1.5% of the general population (Lustmann & Regev, 1990; Williams, 1999).

The pathophysiological mechanism resulting in sialolith formation is not well understood (Lustmann & Regev, 1990; Marchal &

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Dulguerov, 2003). Etiological factors believed to cause salivary stone formation are divided into a few major groups: anatomical variability, salivary composition factors, and hyposalivation (Avishai et al., 2021). It has recently been suggested that different etiologies, namely druginduced sialolithiasis due to hyposalivation versus other etiologies of sialolithiasis have unique characteristics with respect to presentation and treatment outcome (Avishai et al., 2021).

Hyposalivation may result in decreased ductal salivary flow, which can enhance calcium precipitation and sialolith formation. It can result from salivary gland diseases such as Sjögren's syndrome, medications, or without a known etiology (Avishai et al., 2021). Another suspected etiology for salivary stone formation is tobacco smoking. It has been suggested that tobacco smoking might induce salivary duct inflammation, which in turn can cause a decreased ductal diameter, thereby contributing to the development of sialolithiasis (Hammett & Walker, 2022).

The typical mean age at the diagnosis of sialolithiasis ranges from 42 to 51.7. (Huoh & Eisele, 2011; Jin et al., 2020; Sánchez Barrueco et al., 2022; Schrøder et al., 2017) No gender predilection has been determined, as some studies reported higher incidence in men, while others reported more sialoliths in women (Huoh & Eisele, 2011; Jin et al., 2020; Sánchez Barrueco et al., 2022; Schrøder et al., 2017). Changes in serum electrolytes may also contribute to the formation of salivary stones. Since sialoliths are partially composed of calcium and phosphorus, it has been postulated that higher serum concentrations of these electrolytes may increase the incidence sialolithiasis. However, previous studies could not decisively conclude a relationship between electrolyte-modifying medications and sialolithiasis (Marchal & Dulguerov, 2003; Schrøder et al., 2017). Water hardness has also been suggested to be a risk factor for sialolithiasis. Sherman and McGurk (2000) and Schroder et al. (2015) investigated the influence of water hardness and different areas of residency and the occurrence of sialolithiasis. (Schroder et al., 2015; Sherman & McGurk, 2000) Schroder et al. (2015) have found differences in the occurrence of the disease between geographic areas and concentrations of electrolytes, suggesting that environmental or habitual factors may contribute to its development. However, Sherman and McGurk (2000) did not find a correlation between water hardness and sialolithiasis.

Despite the prevalence and clinical implication of sialolithiasis, the current understanding of its characteristics and demographics remains limited. To address this gap in the literature, this study aims to investigate risk factors for sialolithiasis using a big-data retrospective approach.

Insights from this study could enhance our understanding of the pathophysiology of sialolith formation and aid in further development of more effective diagnosis and therapeutic strategies.

2 | METHODS

2.1 | Study design

The data was collected retrospectively from the "Clalit Health Maintenance Organization" (Clalit HMO) database of 2 counties: Dan–Petach-Tikva, Tel-Aviv, and the tertiary hospital of these counties—Rabin Medical Center between 2005 and 2019. Standard International Classification of Disease-10 (ICD-10) coding of sialolithiasis (ICD-10 code K11.5) was used to identify cases of sialolithiasis in the population.

The search protocol included information on patients' complete blood count (CBC) results up to one month before diagnosis with sialolithiasis. The CBC included triglycerides (TG), cholesterol, lowdensity lipoprotein (LDL), high-density lipoprotein (HDL), lipids, and C-reactive protein (CRP), smoking habits, and demographics (including age and gender). Data was received in an anonymized fashion, whereby relevant data was available for each patient, but the name was changed with a random code and the birthdate was randomly assigned to be plus or minus 1 week of the original birthdate. Each sialolithiasis patient was matched with 3 patients who were never diagnosed with sialolithiasis during the registration period (control group). The control group was matched based on age and gender using a nearest neighbor matching algorithm. Considering logistical and clinical challenges, data collection was not uniformly complete across all participants, yielding datasets that were less comprehensive for a select group of individuals.

2.2 | Study group

Inclusion criteria:

- Patients registered at Clalit HMO between the years 2005-2019.
- Age over 22-post discharge from military service.
- Diagnosis of sialolithiasis.

Exclusion criteria:

• Missing blood counts results.

2.3 | Data collection and interpretation

The following variables were collected:

- Age.
- Gender.
- Tobacco smoking—categorized into two categories:
 - Never smoked.
 - Past or present smoker.
- CBC variables:
 - LDL.
 - Total cholesterol.
 - C-reactive protein-divided to two categories based on a threshold of 1 mg/L.
 - HDL.
 - TG.
 - Creatinine.
 - Amylase.
- Body mass index (BMI)

- Socioeconomic status—Participants were categorized into three socioeconomic status groups (low, middle, and high) according to the Israel Central Bureau of Statistics (CBS) classification for socioeconomic status. The CBS classification is based on a composite assessment of demographic composition, educational attainment, standard of living indicators, employment rates, and pension data at the municipal level (Israel CBoSo, 2022).
- Demographic area—Participants were assigned to one of five geographic categories (very peripheral, peripheral, middle, city, and central city) based on the CBS degree of periphery index. This index system assesses a municipal authority's proximity to various opportunities and activities, including markets, employment centers, health services, educational institutions, shopping areas, and leisure facilities (Israel CBoSo, 2020).
- Place of birth.
- Parents born in Israel or not.

2.4 | Statistical analysis

Statistical analyses were conducted using R version 4.3 and R Studio version 2023.3. Descriptive statistics were employed to summarize the data, with means and medians for continuous variables, and frequencies for categorical variables. To determine the distribution

TABLE 1Characteristics of patientswith Sialolithiasis: Complete cohortdescriptive statistics.

of the data, Shapiro-Wilk test was conducted to assess normality. Depending on the outcome of this test, t-tests and Mann-Whitney U tests were applied accordingly. For ordinal variables, chi-squared tests were utilized to assess associations between categorical variables. Lastly, logistic regression analyses were executed in univariate and multivariate levels. A *p*-value of 0.05 > was considered significant.

3 | RESULTS

The cohort was comprised of 20,396 individuals. Out of these, 5100 participants had a diagnosis of sialolithiasis (cases) and 15,296 had no history of sialolithiasis (controls). The mean age at diagnosis was 55.75 ± 17.16 , with females comprising 57.78% of cohort. 35.8% of cohort were past or present smokers, for additional information see Table 1.

The statistical analysis revealed that individuals born in Israel had a significantly elevated risk for having sialolithiasis (57.39% vs 55.75%, p=0.042), additional univariable logistic regression revealed that Israeli born participants had an odds ratio (OR) of 1.06 for having sialolithiasis compared to participants born outside Israel (p=0.042). Additional analysis showed that living in residential areas that were classified as high socioeconomic status was a risk factor

Variable	Subgroup	N	%	М	SD/IQR
Total		20,396	100%		
Sialolithiasis		5100	25%		
Gender	Female	11,784	57.78%		
	Male	8612	42.22%		
Age				55.74	±17.16
Smoking	Now or in past	5285	25.%		
	Never	9745	64.80%		
LDL				108.73	±31.98
Total Cholesterol				184.99	±38.58
CRP				0.38	0.19-1
HDL				49	41-58
TG				114	82-158
Creatinine				0.8	0.67-0.94
Amylase				66	51-86
Socioeconomic Status	Low	1468	7.6%		
Socioeconomic Status	Middle	11,951	61.7%		
Socioeconomic Status	High	5953	30.7%		
Demographic Area	Very Periphery	623	3.1%		
Demographic Area	Periphery	696	3.4%		
Demographic Area	Middle	2918	14.5%		
Demographic Area	City	3446	17.1%		
Demographic Area	Central city	12,505	61.9%		

Note: For normally distributed data, results are presented as means and standard deviations; for non-normally distributed data, results are presented as medians and interquartile ranges (IQR).

for sialolithiasis (33.3% vs 29.9%, p < 0.001), and individuals living in very peripheral, middle, and city areas had significantly more sialolithiasis compared to those living periphery and central city areas (p < 0.001). Moreover, past and present tobacco smoking was identified as risk factor for sialolithiasis (OR=1.46, p < 0.001). See Table 2.

Other significant risk factors were also found in several laboratory measurements. Participants with sialolithiasis had a higher mean triglycerides (117 vs 113, p=0.001) and amylase (69 vs 65, p<0.001). HDL was significantly lower in the sialolithiasis group (48 vs 49, p=0.026), whereas lower LDL values were borderline significantly lower than the control group, (107.9 vs 108.9, p=0.059). See Table 2.

A stepwise multivariable logistic regression revealed that the independent variables predict 4% of the model's variance (Nagelkerke =0.04, H&L>0.05). The model revealed that higher odds of sialolithiasis are among younger patients (OR=0.99, p=0.004), past and present smokers (OR=1.27, p=0.019), and higher amylase (OR=1.007, p<0.001). See Table 3.

4 | DISCUSSION

Sialolithiasis is a benign condition that may result in salivary gland infection, recurrent chronic sialadenitis, abscess, and salivary gland atrophy (Chandak et al., 2012). The results of this study further clarify the characteristics of this disease using a large cohort based on community and hospital-based data.

4.1 | Epidemiological insights into sialolithiasis

The mean age of sialolithiasis at diagnosis was 55.75 ± 17.16 , indicating that this condition is more common among middle-aged individuals than those in advanced age. It is noteworthy that the relatively large standard deviation suggests that this condition may commonly be found among a wide spectrum of ages ranging from approximately 40 to 70 years old. Figure 1 presents the age distribution in patients diagnosed with sialolithiasis, revealing two notable peaks around 30 and 60 years. This pattern may support two hypothesized etiologies for sialolithiasis: Drug-induced sialolithiasis (DIS) and sialolithiasis due to anatomical variations (SAV).

DIS arises from the use of drugs causing hyposalivation, including anticholinergic and sympathomimetic agents, among others. This reduced salivation can lead to diminished saliva flow in ducts, thereby enhancing calcium precipitation and the formation of sialoliths. DIS typically manifests in older patients, characterized by hyposalivation, and a lower incidence of mealtime syndrome. On the other hand, SAV originates from anatomical irregularities in the salivary glands, specifically the hilar region and the ducts. Anatomical variations such as a wide hilus and a convoluted duct may impede saliva flow, thus facilitating mineral precipitation and sialolith formation. Patients with SAV often present at a younger age, have a lower American Society of Anesthesiology (ASA) classification, and require longer intraoperative periods for sialolith removal (Avishai et al., 2021).

The multivariable logistic regression analysis, conducted on a cohort aged 22 to 100 years, indicated that younger individuals have higher risk of developing sialolithiasis (OR. = 0.99, p = 0.004). This finding together with Figure 1 suggests a gradual decline in the likelihood of sialolithiasis with advancing age, possibly due to a diminished impact of risk factors over time. It implies that if risk factors such as anatomical variation, or tobacco smoking use were to contribute to the onset of sialolithiasis, their potential to influence disease development may wane as individuals grow older. Previous studies reported inconclusive results regarding age of onset of sialolithiasis. Schrøder et al. (2017) conducted a population based study, indicating that the mean age at diagnosis was 49.2 ± 18.3 years, Hung et al. (2016) noted that more than 50% of patients were younger than 50 years old, and Jin et al. (2020) reported that about 55% of the cohort was 50-65 years old (Hung et al., 2016; Jin et al., 2020; Schrøder et al., 2017). In our data females had a higher frequency of sialolithiasis than men, similarly, Schrøder et al. (2017) reported significantly higher incidence rate among females (Schrøder et al., 2017). However, other studies reported similar incidence rate between males and females (Hung et al., 2016; Jin et al., 2020).

The results reveal several risk factors associated with area of residency. Participants born in Israel had a significantly higher likelihood to have sialolithiasis, with an OR of 1.06 for sialolithiasis. Individuals living in areas categorized as very peripheral, middle and city areas had significantly more sialolithiasis than those living in other areas. Individuals living in higher socioeconomic communities had significantly higher incidence of salivary stone formation than others. However, these variables did not reach significance as risk factors for sialolithiasis in the multivariable analysis. The influence of environmental factors on sialolithiasis has been a topic of research. Schrøder et al. (2017) found a significant geographical variation in the incidence rate of sialolithiasis (Schrøder et al., 2017). Schroder et al. (2015) reported that different geographic areas were correlated with alterations in water electrolytes which were significantly correlated with higher incidence of sialolithiasis (Schroder et al., 2015). These results reaffirm that sialolithiasis is influenced by geographic and socioeconomic factors. These differences may be due to dietary differences, smoking habits, or drinking water composition and consumption which can be altered due to water minerals, water desalination, domestic water purification devices, or dryer and warmer areas.

4.2 | Lifestyle factors and sialolithiasis

In our cohort, present and past tobacco smoking was a significant risk factor for sialolithiasis. The multivariable logistic regression revealed that the odds of sialolithiasis were higher by 25% among smokers. This finding is consistent with previous studies that reported an increased incidence of salivary stones in smokers (Hung et al., 2016; Jin et al., 2020).

Tobacco smoking can trigger an inflammatory response in the salivary ducts causing swelling and constriction. Consequently, the reduced diameter of the ducts may lead to stasis of saliva flow

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p-value

< 0.001

N.S

N.S

N.S

N.S

< 0.001

< 0.001

p-Value

0.059

N.S

0.06

0.026

0.001

< 0.001

N.S

ABLE 2 Characteristi	cs of patients v	vith Sialolithi	asis: Univar	late statis	tical analysi	s.			
Binary variables									
Variable	9	Subgroup		Sialolithi	asis	Con	trol	Test	
Smoking								OR=1	1.46
	1	Now or in pas	t	1640 (41	.7%)	364	5 (32.8%)		
	1	Never		2294 (58	.3%)	745	1 (67.2%)		
BMI>35				384 (7.6	5%)	114	8 (7.7%)		
Father born in Israel				858 (36	.79%)	446	5 (36.71%)		
Mother born in Israel				891 (39	.06%)	267	7 (40.69%)		
CRP<1				1687 (73	.3%)	405	8 (74.5%)		
Socioeconomic Status								$X^{2} = 1$	9.65
	I	_ow		351 (7.2	2%)	111	7 (7.7%)		
	1	Middle		2893 (59	.5%)	905	8 (62.4%)		
	I	High		1617 (33	.3%)	433	6 (29.9%)		
Demographic Area								$X^{2} = 3$	7.524
	N	Very Peripher	у	182 (3.6	5%)	44	1 (2.9%)		
	I	Periphery		162 (3.2	2%)	53	4 (3.5%)		
	1	Middle		775 (14	.8%)	216	3 (14.3%)		
	(City		985 (19	.4%)	246	1 (16.3%)		
	(Central city		3004 (59%)		950	9501 (62.9%)		
Continuous Variables									
	Sialolithiasis			Control					
	М		SD/IQR		М		SD/IQR		Test
LDL	107.9		31.34		108.9		32.2		т
Total Cholesterol	131.84		71.37		128.76		70.49		Т
BMI	26.48		23.4, 29.7		26.22		23.3, 29.9		M.W
HDL	48		40, 58		49		41, 58		M.W
TG	117		84, 159		113		82, 157		M.W
Creatinine	0.79		0.68, 0.94		0.8		0.67, 0.94		M.W
Amylase	69		52, 90		65		50, 85		M.W

Note: Depending on the normality of the data, either t-tests or Mann-Whitney U tests were performed. For normally distributed data, results are presented as means and standard deviations; for non-normally distributed data, results are presented as medians and interguartile ranges (IQR).

TABLE 3 Stepwise multivariable logistic regression to assess the odds for sialolithiasis.

	OR	CI	p-value
Age	0.99	0.983-0.997	0.004
Smoking (Past and present)	1.247	1.037-1.499	0.019
Amylase	1.007	1.005-1.01	<0.001

Note: Variables that were assessed are: gender, place of birth, smoking, CRP>1, amylase, TG, LDL, HDL, BMI, and age.

and the development of sialolith. The obstruction can diminish salivary flow and provide an environment for retrograde bacterial infection exacerbating the formation of stones (Harrison, 2009). Furthermore, prolonged tobacco smoking reduces salivary flow, further accelerating the formation of sialolithiasis (Rad et al., 2010).

BMI was a borderline significant risk factor for sialolithiasis (p=0.06), as higher BMI was correlated to sialolith formation. Jin et al. (2020) performed a study of 947 sialolithiasis participants to investigate the association between the disease and obesity. They concluded that BMI did not show any difference in the incidence rate (Jin et al., 2020). Additionally, we also found differences in the levels of lipids in the CBC. HDL was significantly lower in the sialolithiasis group, whereas TG was significantly higher. In addition, LDL was lower, but the statistical tests did not reach significance (p=0.059). However, these variables did not reach significance as risk factors for sialolithiasis in the multivariable analysis. Abnormal lipid levels had been correlated with impaired salivary flow (Izumi et al., 2000; Mizoguchi et al., 2023). Reduced salivary flow rate can





lead to stasis and supersaturation of saliva, promoting the precipitation of calcium salts and subsequent formation of sialoliths within the salivary ducts.

4.3 | Biochemical and clinical parameters

The multivariable logistic regression analysis revealed that higher amylase levels increase the odds of sialolithiasis by 0.7% for each unit increase in serum levels. Serum amylase exists in two isoforms: the P type, secreted by the pancreas, and the S type, secreted by the salivary glands. Approximately 55% to 60% of serum amylase is secreted from the salivary glands. Elevated serum amylase levels are commonly associated with the release of amylase into the serum by a diseased organ, such as an obstructed salivary gland (Argiris et al., 1999; Peyrot Des Gachons & Breslin, 2016; Pieper-Bigelow et al., 1990). This finding suggests that prior to the acute phase of sialolithiasis, the salivary gland may initiate a mild inflammatory response, as indicated by the differences observed in this study, including the rise in serum amylase levels and the increased odds for sialolithiasis.

The limitations of this study are due to its retrospective and big-data nature. Data was collected retrospectively without human intervention through ICD-10 coding, which did not allow the collection of additional confounding factors (such as physical activity, family history, tobacco smoking pack-year, dietary habits, glad location, sialolith size, or method of treatment) that were manually recorded.

5 | CONCLUSIONS

This big-data study of 5100 patients with sialolithiasis revealed that the average age at diagnosis was 55.75 years, with a higher prevalence among women. Several factors related to geographic location emerged as significant risk factors. These included being born in Israel, residing in peripheral, middle, or city areas, and living in higher socioeconomic communities. Additionally, lifestyle factors such as tobacco smoking, as well as metabolic conditions like hyperlipidemia and elevated body mass index (BMI), were also associated with increased risk. Patients with sialolithiasis exhibited higher levels of amylase.

This study provides valuable insights into the demographic and laboratory characteristics of sialolithiasis patients in a big data cohort. The findings may contribute to a better understanding of the disease and the development of preventative measures or early diagnostics tools.

AUTHOR CONTRIBUTIONS

Ehud Jonas: Investigation; validation; writing – review and editing; visualization; formal analysis; writing – original draft. Daniel Muchnik: Writing – review and editing; validation. Idan Rabinovich: Writing – review and editing; writing – original draft; investigation; data curation. Daya Masri: Validation; writing – review and editing. Gavriel Chaushu: Conceptualization; investigation; methodology; writing – review and editing; supervision. Gal Avishai: Conceptualization; investigation; writing – original draft; methodology; validation; writing – review and editing; visualization; formal analysis; project administration; supervision; resources.

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None.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

Research data are not available due to privacy restrictions.

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