Do high levels of Amylase following laparoscopic sleeve gastrectomy predict devastating complications?

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Research article

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Abstract

Background

Gastric leak post laparoscopic sleeve gastrectomy (LSG) is a severe complication that may lead to sepsis and even to patient's death. Early diagnosis and treatment are critical. It was hypnotized that the appearance of high levels of amylase, especially in the drain, may indicate a leak from the gastric staple line. The purpose of this prospective study was to examine the incidence of Amylase increase in the blood, urine and drain fluid, after LSG and to examine whether the appearance of high levels of Amylase indicates the existence of a major complication and especially a leak from the staple line.

Methods

From 161 patients whom underwent Sleeve gastrectomy, we prospectively evaluated the demographic information, including Body-mass-index (BMI), comorbidities, complications during the surgery or hospitalization, laboratory data including complete blood count, liver function tests, glucose and Amylase levels in blood, urine and drain. Testing for the normal distribution of the variables was performed using Kolmogorov-Smirnov test. Based on the results of this test we performed T- test or Mann-Whitney test to find differences between groups. Multivariate analysis using logistic regression was performed to examine the independent variables which can predict a rise in Amylase values above the upper limit number (ULN).

Results

Of 161 patients in this study, 35 patients (21.8%) had a rise in the Amylase values in blood, urine and/or drain, and 126 patients (78.2%) had normal values of Amylase until discharge. Amylase rise has been found to be correlated with Neutrophilia (OR = 5.4, p = 0.003), indirect hyperbilirubinemia (OR = 3.9, p = 0.022) and a decline in phosphate level (OR = 2.48, p = 0.019). Furthermore, a rise in Amylase is significantly associated to a rise in Aspartate and Aspartate transaminase transaminases (AST and ALT), Gamma-Glutamyl Transferase (GGT), Creatine-phosphokinase (CPK), Glucose and leukocytes, and a decline in lymphocytes and Calcium. No significant change was found in the duration of the operation and neither in the length of hospitalization. No specific complication was found to be significantly higher in any of the groups. One patient suffered from staple line leak and was treated conservatively. The diagnosis was done in post- operative day three by abdominal CT-scan. The amylase levels in the blood and the drain were normal and only a slight increase of amylase in urine was measured.

Conclusions

Increase in Amylase after LSG doesn't necessarily indicate a major complication such as staple line leak and in the vast majority of cases, it seems to have no clinical relevancy. Therefore, it should not automatically lead to a full clinical investigation in the absence of further clinical signs. Our results suggest that there is no clinical justification for Amylase tests in any method after LSG.

Background

Obesity, especially morbid obesity, is associated with prevalence of a variety of health problems, including type 2 diabetes, hypertension, coronary artery disease, many forms of cancer and cognitive dysfunction [1], as well as being associated with negative social effects. A number of weight-loss surgical methods have been developed and are often used after the patient has tried to lose weight using weight loss diets, exercise and weight loss medications. One of the surgical methods is Laparoscopic Sleeve Gastrectomy (LSG). LSG has a risk of complications which is around 6.3%, the major complications are 2.4% and declining along the years. Common short-term post-op complications are bleeding occurring in 1.8% of cases, high leaks (near the esophagogastric junction) occurring in 1.1%, stenosis occurring in 0.9% and mortality rate is around 0.33% [2–18].

Alfa-Amylase is an isoenzyme that is produced especially in both the pancreas (P type, which is also found in the bile) and the salivary glands (S type) as different forms [19], but the most of the commercial laboratory kits cannot distinguish between them. In our hospital Amylase is measured in Somogyi International Units (IU). Its usual value in the saliva is around 70,000 IU/L, so a simple calculation can show us that every 1 mL of saliva contains 700 IU of Amylase. Hence, any contact between the saliva, which is inside the lumen of the digestive system, and the blood stream, like for example when cutting the digestive tract in LSG or in a leak of the tract, may rise the Amylase amount in the blood test. Since Amylase is being excreted in the urine, it may raise in the urine tests. The pancreas may also leak Amylase into the blood stream if it is damaged [20, 21]. Amylase from the biliary tree, from both intra and extra-hepatic parts, can also be released into the blood after a liver or biliary injury and may also raise Liver function tests [22].

According to that, the absence of Amylase in the drain left in the surgery bed may help rule out an option of a leak. Maher et al. already suggested a cut-off point of 400 IU/L of Amylase in the drain after Roux-en-Y procedure, that below it the sensitivity is 94.1% and the specificity is 90% for ruling out a leak [23]. However, any value above 400 IU/L cannot rule in such a leak, since Amylase is not sensitive nor specific enough.

In some of our patients who underwent LSG, high levels of amylase either in blood tests, urine tests and/or drain fluid analysis had been detected, followed by a rapid decline to normal value.

The first objective of our study was to determine the prevalence increase of amylase in the blood, urine or drain fluid. The second objective was to try to find a correlation between this rise and any complication during the operation or during the perioperative era, and especially to find out if Amylase rise can be a good sign of leaks.

Methods

One hundred sixty-one patients underwent LSG during one year in Rambam Medical Center were included prospectively in the study. All the patients were extensively informed concerning the surgery and provided written informed consent. The study was approved by the Ethics Committee of Rambam Medical Center Institution.

Surgical technique was standardized in all patients using 38 French bougie and disposable linear cutter stapler, without buttressing, oversewing or reinforcing of the staple-line and without a routine intraoperative leak test nor routine postoperative UGI contrast studies. At the end of the operation a Jackson-Pratt drain is placed along the staple line. Each patient had an extensive preoperative evaluation, including demographic information and medical background– Gender, BMI, comorbidities, eating habits and regular medication. Laboratory data before and after the procedure, including Complete Blood Count, Aspartate and Aspartate transaminase transaminases (AST and ALT), Gamma-Glutamyl Transferase (GGT), Creatine-phosphokinase (CPK), Alkaline-phosphatase (ALK), direct and indirect Bilirubin, Sodium, Potassium, Calcium and Phosphate was measured. Amylase level in the blood, urine and drain fluid was tested. Baseline blood tests were taken and were checked before the LSG. All tests were taken on a daily basis starting on the next mornings until discharge.

Testing for normality of the variables was performed using Kolmogorov-Smirnov test. Based on the results of this test we performed T- test or Mann-Whitney test for differences between groups.

Linear correlations between continued variables were tested using Pearson correlation.

Multivariate analysis was performed using logistic regression in order to examine the independent variables which can predict a rise in Amylase values above upper limit number (ULN). To help reduce the influence of multicollinearity, for the multivariate analysis, the independent variables were chosen according to the mentioned univariate tests of T- test and Mann-Whitney test and according to the strength of the correlation (r) between the continuing variables of the correlation tests.

The statistical significance was chosen to be a P-Value of 0.05.

All calculations were done in SPSS (Statistics Products Solutions Services) platform.

Results

In our hospital, the ULN of Amylase is 140 IU/L in the blood and the drain and 600 IU/L in the urine and. Of 161 patients in this study, 35 patients (21.8%) had a rise in the Amylase values in blood, urine and/or drain, and 126 patients (78.2%) had normal values of Amylase until discharge. As summarized in Table 1, regarding the demographic information and medical background of the patients, no significant change between the groups of normal Amylase and the high Amylase was found. The sum of each laboratory tests is written in Table 2.

Table 1
Demographic data and medical background

	Normal Amylase N = 126 (78%)	High Amylase N = 35 (22%)	P-Value
Age	13.09 ± 39.13	11.00 ± 38.49	NS
Female	92 (73%)	31 (88%)	P = 0.07
Body mass index	4.32 ± 43.18	4.29 ± 43.23	NS
Diabetes Mellitus	26 (21%)	11 (31%)	NS
Hypertension	35 (28%)	6 (17%)	NS
Hypothyroidism	7 (6%)	4 (11%)	NS
Hyperlipidemia	24 (19%)	6 (17%)	NS
Abdominal surgery in past	25 (20%)	11 (31%)	NS
Smoking	29 (23%)	8 (23%)	NS
Taking NSAIDS frequently	12 (9%)	1 (3%)	NS

Table 2
– Laboratory Amylase samples – average value with SD and number of samples

	Normal Amylase	Amylase above ULN	Total
Blood Amylase > 140 IU/L	47.63 ± 18.33 IU/L N = 259	341.67 ± 125.02 IU/L N = 3	262 blood samples
Urine Amylase > 600 IU/L	191.28 ± 116.86 IU/L N = 141	843.42 ± 202.44 IU/L N = 12	175 urine samples
Drain Amylase > 140 IU/L	51.74 ± 33.18 IU/L N = 149	428.04 ± 456.75 IU/L N = 26	153 drain samples
Total samples	549 normal samples	41 abnormal samples	590 samples

One patient (0.6%) had a concurrent increase in Amylase values in the drain and the blood. One patient (0.6%) had an Amylase rise in the drain, which lasted for a day, and had an Amylase rise in urine three days afterwards. Except those two patients, all other 33 patients had an Amylase rise only in one of the three measured methods.

As summarized in Table 3, no surgery needed to be converted from laparoscopic surgery to laparotomy and no intra-operative complications have occurred, no significant change was found in the duration of

the operation and neither in the length of hospitalization, and no specific complication was found to be significantly higher in any of the groups.

Table 3
– Operation duration and peri-operative major complications.

	Normal Amylase group N-126 (78%)	High Amylase group N = 35 (22%)	P-Value
Surgery duration (minutes)	50 ± 12.2	66 ± 20.4	NS
Intra-operative complication	(0%)0	(0%) 0	NS
A leak	(0%)0	(2.8%) 1	NS
Bleeding	(3.2%) 4	(0%)0	NS
Fever from unknown origin	(0.8%) 1	(2.8%) 1	NS
Pyelonephritis	(0.8%) 1	(0%) 0	NS
Fever from peripheral line phlebitis	(0.8%) 1	(0%) 0	NS
Length of hospitalization (days)	3.70 ± 0.12	3.28 ± 0.18	0.57
NS = No statistical significance (P value > 0.1).			

Regarding six of the patients (3.7%) there was a suspected leak peri-operatively due to: fever of unknown origin (the two who were mentioned above), relevant pathologic signs on physical examination, and/or extreme increase in Amylase value in either blood, urine or drain. All those patients received oral methylene blue dye which was not shown afterwards in the drain. Because of continuing high suspicion in two patients, they also went through a CT-scan which didn't reveal any leak.

One of these patients (0.6%) suffered from fever of 39^{O}_{C} three days postoperatively. Physical examination revealed pus draining from the surgical wound and the Amylase in the urine became high. Upper GI series was normal and two Methylene blue dye swallows didn't reveal sign of a leak. The patient underwent a wound opening which drained a lot of pus and the fever went down to 37.7^{O}_{C}. He was put on nil-per-os, parenteral nutrition and antibiotics. Gastroscopy was done, revealing a tiny fistula in the stomach and closing it with a clip. The patient felt good after the procedure and the leak stopped. The patient was eventually discharged resuming normal oral intake. During One-year follow up, no evidence of leak or fistula was noted, and the patient resumed normal daily life.

All the values that had a statistically significant difference as mentioned in Table 4, have been forwarded to multivariate analysis according to Pearson's correlation coefficient, with the following exceptions:

Table 4
– The averages of the specific laboratory value and a concomitant rise of Amylase above and pathologic value of the specific laboratory test

Laboratory value (it's units)	Normal Amylase group N-126 (78%)	High Amylase group N = 35 (22%)	P-Value	Concomitant pathologic value	P-Value
WBC (cells/mm^3)	11.28	13.08	P = 0.013	16.1%±	P = 0.011
HGB (g/L)	12.78	12.34	NS	11.7%§	NS
%HCT (Percent)	38.84	37.42	NS	12.9%§	NS
Platelets (1000cells/mm^3)	260.96	248.84	NS	0%§	NS
%RDW (Percent)	14.13	14.07	NS	10.5%±	NS
Neutrophils (cells/mm^3)	8.16	11.09	P < 0.001	18.9%±	P = 0.004
Lymphocytes (cells/mm^3)	1.99	1.63	P = 0.031	19.4%±	NS
% Neutrophils	70.25	79.51	P < 0.001	21.8%±	P < 0.001
% Lymphocytes	20.85	12.85	P < 0.001	21.8%±	P < 0.001
Glucose (mg/dL)	117.92	135.50	P = 0.002	16.7%±	P = 0.006
Potassium (mEq/L)	4.10	3.98	NS	37.5%§	P = 0.051
Sodium (mEq/L)	137.74	137.00	NS	0%§	NS
Calcium (mg/dL)	8.74	8.29	P = 0.002	15.9%§	NS
Inorganic Phosphate (mg/dL)	3.33	2.93	P = 0.005	26.9%§	P = 0.067

± - from the cases when Amylase is above ULN, the percentage of cases when the specific value is also above ULN. § - from the cases when Amylase is above ULN, the percentage of cases when the specific value is below LLN. NS = No statistical significance (P value > 0.1). WBC - White Blood Cells. RBC - Red Blood Cells. HGB - Hemoglobin. %HCT - %Hematocrit. MCV - Mean corpuscular volume. MCHC - Mean corpuscular hemoglobin concentration. %RDW - % Red blood cell distribution width. BUN - Blood Urea Nitrogen. ALK - Alkaline Phosphatase. AST - Aspartate Transaminase. ALT - Alanine Transaminase. GGT - Gamma-Glutamyl-Transferase. LDH - Lactic Acid Dehydrogenase. CPK - Creatinine Phospho Kinase.

Laboratory value (it's units)	Normal Amylase group N-126 (78%)	High Amylase group N = 35 (22%)	P-Value	Concomitant pathologic value	P-Value
BUN (mg/dL)	10.39	9.00	NS	0%±	NS
Creatinine (mg/dL)	0.66	0.62	NS	11.1%±	NS
ALK (U/L)	93.53	86.36	NS	16.7%±	NS
AST (IU/L)	30.77	63.04	P = 0.008	19.2%±	P = 0.039
ALT (IU/L)	53.48	93.64	P = 0.005	21.8%±	P = 0.032
GGT (U/L)	46.45	81.14	NS	21.3%±	P = 0.048
LDH (U/L)	216.67	240.59	NS	14.9%±	NS
CPK (ng/mL)	152.69	435.00	P = 0.040	20.7%±	NS
Bilirubin – total (mg/dL)	0.56	0.67	P = 0.044	25%±	P = 0.046
Bilirubin - direct (mg/dL)	0.12	0.14	NS	19.2%±	NS
Bilirubin - indirect (mg/dL)	0.40	0.53	P = 0.037	25%±	P = 0.026
BUN/CR (no units)	15.98	14.77	NS	9.4%±	NS

± - from the cases when Amylase is above ULN, the percentage of cases when the specific value is also above ULN. § - from the cases when Amylase is above ULN, the percentage of cases when the specific value is below LLN. NS = No statistical significance (P value > 0.1). WBC - White Blood Cells. RBC - Red Blood Cells. HGB - Hemoglobin. %HCT - %Hematocrit. MCV - Mean corpuscular volume. MCHC - Mean corpuscular hemoglobin concentration. %RDW - % Red blood cell distribution width. BUN - Blood Urea Nitrogen. ALK - Alkaline Phosphatase. AST - Aspartate Transaminase. ALT - Alanine Transaminase. GGT - Gamma-Glutamyl-Transferase. LDH - Lactic Acid Dehydrogenase. CPK - Creatinine Phospho Kinase.

WBC, Neutrophils count and percentage, all have a Pearson's correlation of around r = 0.95, and Lymphocytes count and percentage have opposite significant correlation, but from all, Neutrophils percentage have the highest Pearson's correlation - r = 0.973, and hence it was chosen for the multivariate analysis.

Secondly, Indirect Bilirubin has a Pearson's correlation of r = 0.968 with Total Bilirubin. Since there was no significance change in direct bilirubin, the Indirect Bilirubin has been chosen for the multivariate analysis

from the indirect and total Bilirubin.

According to the multivariate analysis, four variants have been found to have significant correlation to concurrent rise in Amylase above the ULN as follows:

1. Any rise in 1% in Neutrophils has an odds ratio of concurrent rise in Amylase of 1.11 (p=0.001, 95% CI=1.05-1.18), and a rise above ULN of neutrophils, which in our laboratory is 73.2%, has an odds ratio of 5.4 (p=0.003, 95% CI=1.74-16.48) of concurrent rise in Amylase above ULN.
2. A rise in indirect bilirubin above ULN, which in our laboratory is 1mg/dl, has an odds ratio of 3.9 (p=0.022, 95% CI=1.21-12.5) of concurrent rise in Amylase above ULN.
3. Any decline of 1mg/dl in phosphate level has an odds ratio of concurrent rise in Amylase of 2.48 (p=0.019, 95% CI=1.16-5.26).

Although a rise in Amylase is significantly associated with a rise in AST, ALT, GGT, CPK, Glucose and Calcium as mentioned in Table 4, the multivariate analysis could not find any strong correlation between them.

Discussion

As mentioned in Tables 1 and 3, the patients who had a rise in Amylase values didn't differ from the patients who had normal Amylase values in preoperative variables including demographic data or medical background details, as mentioned in other studies [14, 24], nor in surgery complications, surgery duration, peri-operative complications nor length of stay in the hospital.

As for the laboratory tests, which were found to have significant correlation to the rise in the Amylase, we can make a few hypotheses.

First of all, a rise in Amylase has been found to be significantly associated with a concurrent rise in ALT, AST and GGT above the ULN, without any change in ALK nor conjugated bilirubin, what defines this change as hepatocellular change. All these may point to a liver injury during the procedure, which is able to increase the Amylase values [25–28]. During the operation, a retraction of the liver towards the abdominal wall by a retractor is necessary to allow good visibility of the stomach. Such a minimal liver injury, which expressed only in a little laboratory change, seems not to have any clinical significance.

A rise in Amylase has also been found to be significantly correlated to a rise in Creatinine Phospho-Kinase (CPK). The common reason to a CPK raise is muscle injury, either from the heart, which has been excluded since we didn't experience a concurrent rise in Lactate dehydrogenase (LDH), or from an injury to the abdominal wall muscles from its cutting during the surgery. Such rise may also occur due to acute renal failure, which has been ruled out since there was no concurrent change in Creatinine nor Blood-urea-nitrogen (BUN); It may also happen in an injury to the brain, testicles, retina or inner ear, which has no connection to LSG, and in pancreatitis [29–31]. Such mild pancreatitis may be created from the separation of the stomach from the pancreas during the surgery and it may also happen due to the

medications were given during the procedure [32]. Bariatric surgery has already been connected to a higher tendency of the pancreas to produce pancreatitis [8, 33]. Furthermore, a rise in Amylase has been found to be significantly correlated to a rise in Glucose, and such concomitant rise can reflect the a greater body stress in the patients who experienced Amylase rise or also be created from pancreatitis since pancreatitis decreases the amount of secreted insulin [34, 35]. Moreover, a rise in Amylase above ULN has significant association to a decrease in the levels of Calcium and a significant correlation to a decrease in the levels of Phosphorus, which are both known to be correlated to pancreatitis [36–38]. It should be noted that during this study we didn't measure the level of Lipase, even though its' better sensitivity and specificity of pancreatitis. Nevertheless, such pancreatitis seems to be minimal and with no clinical significance.

In addition, a rise in Amylase has been found to be significantly associated with a concurrent rise in white-blood-cells count (WBC) which expressed via a rise in Neutrophils count and percentage and a decline in the counts and percentage of Lymphocytes. This change may be attributed to a release of inflammatory mediators from either the damaged liver or pancreas as described above.

A rise in Amylase has also been found to be significantly correlated to a rise in Indirect Bilirubin, without a change in Direct Bilirubin. Increasing evidence that indirect bilirubin stimulates Amylase release from the pancreas [39, 40]. As for the origin of this indirect bilirubin raise, we didn't check Haptoglobin, glucose-6-phosphate-dehydrogenase (G6PD) deficiency, Reticulocyte count nor peripheral blood smear, but we didn't reveal any LDH rise, Red-Cell-Distribution-Width (%RDW) rise or Hemoglobin decline, what implies that the probability that the unconjugated bilirubin comes from hemolysis is not very high. We have no good reason to believe that in this study we had a high percentage of patients with syndrome such as Gilbert syndrome that can explain this phenomenon. A better option is that it may come from a hematoma which might happen in LSG to one of the intra-abdominal organs, such as the liver or the pancreas as already been hypothesized above, or an intra-mural hematoma inside the abdominal wall muscles due to their cutting.

A leak may be the most feared complication when observing a peri-operative Amylase rise, since in two thirds of cases it may lead to sepsis and even to patient's death [18, 41], and hence it may be critical to diagnose this complication and treat accordingly. This complication is contributed especially to a long staple line and high intraluminal pressure, and also to ischemia, hematoma formation, and staple misfiring. According to The American Society for Metabolic and Bariatric Surgery's recommendations [42, 43], intraoperative leak may be discovered using endoscopy and/or distention of the anastomosis with dye, air, or other gas. Post-operative suspicion may be proceeding using abdominal CT, with or without a chest CT, or reexploration [42–48]. Despite gathering information about factors that are associated with an increased risk of a leak, and different ways to reduce this risk that have been offered, due to the heterogeneity of the studies and small statistical power there are still no recommendations of ways to prevent leaks [18, 42, 43, 49].

During the study, one complicated event ended with a leak as mentioned above, but it was revealed not because of the high-Amylase the patient had, but due to Systemic inflammatory response syndrome (SIRS) and especially hyperpyrexia, as already noted by other studies [41, 44, 50]. The Amylase in the urine became high but not in the blood nor the drain. It should be mentioned that the value of the Amylase was 147% of ULN which is much less than other hyperamylasurias we observed during the study without a leak. The diagnosis was done finally by gastroscopy.

Hence, although the non-specific hyperamylasuria, other clinical signs may be more helpful in recognition of such a leak. Furthermore, blood Amylase wasn't sensitive at all in this case. Since we did not experience a leak into the peritoneal cavity, we cannot conclude about the useful of drain Amylase in such leaks, but even though a lot of organized fistulas start as an open leak, we didn't observe Amylase raise in the drain before the occurrence of the fistula, what may imply that Amylase in the drain is not sensitive enough for small leaks. Except of this patient, during the study we didn't experience any leak even when there was a high suspicion, for example due to an Amylase rise.

Moreover, the total amount of complications was lower in the high-Amylase group than in the normal-Amylase group. In consequence, Amylase rise is not suitable to be a non-specific sign for complications other than leak.

An increase in Amylase seems not to be specific enough for a leak, since in the vast majority of cases, a rise in Amylase may be associated with hepatic and/or pancreatic manipulation which has no clinical significance. Also, blood Amylase is not sensitive for a leak, and drain Amylase may not be sensitive for small leaks. Even in the appearance of a leak, other methods may be helpful enough for revealing leaks without the need for urine Amylase. Hence, an Amylase test may have a no clinical justification of being taken.

Limitations of this study include a relatively small number of patients for detection of a clear trend in those with leakage, due to the low incidence of leak. Regardless of the fact that our study shows clearly that even though amylase levels were high in more than one fifth of patients, it has no clinical significance in the absence of appropriate clinical context. In addition, since pancreatitis may explain the rise in Amylase, a repeat on such research should include Lipase test and/or urine Amylase-to-Creatinine Clearance-Ratio to confirm or to refute this option.

Conclusions

This study found no correlation between leaks and Amylase rise, but did indeed find a correlation to what may be hepatic or pancreatic damage or hematoma, but without any clinical significance.

It can be suggested that an isolated rise in Amylase in any method should not automatically lead to a clinical investigation in the absence of further clinical signs of any complication.

Therefore, this study did not reveal any clinical justification for routine Amylase tests in any method after LSG.

Abbreviations

NS = No statistical significance.

WBC - White Blood Cells.

RBC - Red Blood Cells.

HGB - Hemoglobin.

%HCT - %Hematocrit.

MCV - Mean Corpuscular Volume.

MCHC - Mean Corpuscular Hemoglobin Concentration.

%RDW - % Red blood cell Distribution Width.

BUN - Blood Urea Nitrogen.

ALK - Alkaline Phosphatase.

AST - Aspartate Transaminase.

ALT - Alanine Transaminase.

GGT - Gamma-Glutamyl-Transferase.

LDH - Lactic Acid Dehydrogenase.

CPK - Creatinine Phospho-Kinase.

G6PD - Glucose-6-Phosphate-Dehydrogenase.

SIRS - Systemic Inflammatory Response Syndrome.

LSG – Laparoscopic Sleeve Gastrectomy.

BMI – Body Mass Index.

ULN – Upper Limit Number.

LLN – Lower Limit Number.

Declarations

Ethics approval and consent to participate

Informed consent was obtained from all the individual participants included in the study.

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

The study was approved by Rambam institution of health Helsinki committee, reference number 0090-11-RMB.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors contributed to the study and to the article, reviewed the manuscript and approved the final version for publication.

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