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Vomiting and Hyponatremia Are Risk Factors for Worse Clinical Outcomes Among Patients Hospitalized Due to Nonsurgical Abdominal Pain

A Retrospective Cohort Study

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Abstract: After initial evaluation in the Emergency Department (ED), many patients complaining of abdominal pain are classified as suffering from nonsurgical abdominal pain (NSAP). Clinical characteristics and risk factors for worse prognosis were not published elsewhere.

Characterizing the clinical profile of patients hospitalized due to NSAP and identifying predictor variables for worse clinical outcomes.

We made a retrospective cohort analysis of patients hospitalized due to NSAP compared to matched control patients (for age, gender, and Charlson comorbidity index) hospitalized due to other, nonsurgical reasons in a ratio of 1 to 10. We further performed in-group analysis of patients admitted due to NSAP in order to appreciate variables (clinical and laboratory parameters) potentially associated with worse clinical outcomes.

Overall 23,584 patients were included, of which 2144 were admitted due to NSAP and 21,440 were matched controls. Patients admitted due to NSAP had overall better clinical outcomes: they had lower rates of in-hospital and 30-days mortality (2.8% vs 5.5% and 7.9% vs 10.4% respectively, $P < 0.001$ for both comparisons). They also had a significantly shorter length of hospital stay (3.9 vs 6.2 days, $P < 0.001$). Rates of re-hospitalization within 30-days were not significantly different between study groups. Among patients hospitalized due to NSAP, we found that vomiting or hyponatremia at presentation or during hospital stay were associated with worse clinical outcomes.

Compared to patients hospitalized due to other, nonsurgical reasons, the overall prognosis of patients admitted due to NSAP is favorable. The combination of NSAP with vomiting and hyponatremia is associated with worse clinical outcomes.

(*Medicine* 95(14):e3274)

Abbreviations: ALP = alkaline phosphatase, ALT = alanine transaminase, BMI = body mass index, CHF = congestive heart failure, COPD = Chronic Obstructive Pulmonary Disease, CRP = C-reactive protein, ED = emergency department, EMR = Electronic Medical Records, FMF = familial mediterranean fever, GFR = glomerular filtration rate, HR = hazard ratio, LDH = lactate dehydrogenase, NSAP = nonsurgical abdominal pain, SD = standard deviation, SGPT = serum glutamic pyruvic transaminase, WBC = white blood cells.

Editor: Xu-jie Zhou.
Received: January 7, 2016; revised: March 1, 2016; accepted: March 7, 2016.
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The authors have no funding and conflicts of interest to disclose.
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ISSN: 0025-7974
DOI: 10.1097/MD.0000000000003274

INTRODUCTION

Abdominal pain is a common, yet challenging complaint among patients presenting to the hospital.[1,2] The initial investigation in the Emergency Department (ED) is often intended to rule out acute or surgical causes of the abdominal pain. However, in up to 30% of cases, the etiology of abdominal pain remains unclear even after adequate investigation,[3] and many of these patients require further, in-hospital investigation, and are classified as nonsurgical abdominal pain (NSAP). Currently, there are no published data regarding the clinical characteristics nor known risk factors for worse clinical outcomes in this large patient population.

The primary goal of this study was to characterize hospitalized NSAP patients, compared to patients hospitalized due to other, nonsurgical problems and to identify risk factors associated with poor clinical outcomes (such as short-term mortality and rehospitalization).

PATIENTS AND METHODS

In this retrospective study we compared patients admitted to general medicine departments due to NSAP with matched controls to the same hospital departments due to other, nonsurgical complaints. All these patients were initially evaluated in the ED, by a surgeon, an internist or an emergency physician, and it was deemed appropriate that there was no need for further surgical intervention or evaluation. However, these patients were not discharged home, but rather hospitalized, with the purpose to further evaluate the cause of the abdominal pain, or treat an underlying, nonsurgical cause.

Our work is based on a registry of Electronic Medical Records (EMR) of admissions to the Chaim Sheba Medical Center, the largest tertiary medical center in Israel, between the years 2007 and 2013. We screened a total of 129,431 medical records corresponding to hospitalizations of patients aged 18 years or more, of whom, 2144 patients were identified as being admitted due to NSAP and 21,440 other patients were identified as their matched controls. We matched each patient admitted due to NSAP to control patients selected for having the same gender, age, and comorbidity level (as assessed by the Charlson

co-morbidity score)[4] using *MatchIt for case matching*.[5] The Charlson score was calculated using ICD-9 diagnoses codes recorded at the time of admission. We extracted medical records from the Chameleon system database (Elad Healthcare Solutions) and used the national ID number of patients to obtain mortality information from the National Israeli Population Registry.[6] Data collection was performed using SQL and custom Python/Pandas scripts. Statistical analyses were performed in R Statistical Language (R 2.1.15). We used the Mann–Whitney *U* test to detect significance for ordinal features, and the Fisher Exact test for categorical features.

The study was approved by the Chaim Sheba Medical Center (Ramat Gan, Israel) Institutional Ethics Committee (approval number SMC-0568-13, September 12, 2013). Patient information was anonymized and deidentified prior to data analysis.

RESULTS

Overall, patients admitted to general medicine for abdominal pain were younger (64.5 ± 20.0) than the control patients (70.4 ± 16.7) and included a greater proportion of females (57% vs 48%). In order to reduce the effect of these differences, we matched the 2144 patients who were admitted due to NSAP with 21,440 control patients admitted for other, variable causes, and had the same age, gender, and Charlson comorbidity index. Table 1 describes the baseline characteristics and clinical endpoints of both study groups. By design, the 2 groups have similar proportion of female patients, age, and comorbidity level. Likewise, associated diagnoses such as metastatic malignancy, diabetes mellitus, and ischemic heart disease were comparable between the groups. Of note, patients in the control group had significantly more congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), and dementia. Laboratory parameters that did not differ significantly between study groups were total bilirubin concentration, amylase, serum glutamic pyruvic transaminase (SGPT), and sodium levels.

As one could expect, gastrointestinal diseases were significantly more prevalent at admission among patients admitted to general medicine departments due to NSAP: peptic ulcer disease (1.8% vs 0.4%, $P < 0.001$); inflammatory bowel disease (1.2% vs 0.3%, $P < 0.001$), colon and pancreatic cancer (0.65% vs 0.31%, $P < 0.05$ and 0.56% vs 0.11%, $P < 0.001$); familial mediterranean fever (FMF) (1.3% vs 0.1%, $P < 0.001$), and chronic liver disease (2.3% vs 1.1%, $P < 0.001$). Background diagnoses that were significantly less prevalent among patients admitted to general medicine departments due to NSAP were congestive heart failure (CHF) (1.8% vs 4.2%, $P < 0.001$) and chronic obstructive pulmonary disease (COPD) (1.0% vs 2.2%, $P < 0.001$). As detailed in Table 1, laboratory values including (ALP (Alkaline Phosphatase, IU/L) and LDH (Lactate Dehydrogenase, IU/L), (119 vs 112 and 294 vs 288, $P < 0.05$ and $P < 0.001$ respectively) were higher among NSAP patients compared to those values for Troponin I (mcg/L) and CRP (C-reactive protein, mg/L), (0.176 vs 0.457 and 48.7 vs 61.8, respectively, $P < 0.001$ for both comparisons) in this same group of patients.

The average length of hospital stay turned out to be shorter for patients admitted with NSAP compared to their matched control group patients (3.92 vs 6.16 days, $P < 0.001$). Death during hospital stay was significantly lower in the NSAP group compared to their matched control group (2.8% vs 5.5%, $P < 0.001$). Both 30-day and 1-year mortality rates were also lower in the NSAP group compared to controls (7.9% vs 10.4%, $P < 0.001$ and 22.5% vs 25.5%, $P < 0.05$). The Kaplan–Meier survival rate of both study groups is presented in Figure 1. The rate of rehospitalizations within 30 days did not differ significantly between the study groups although NSAP patients had significantly lower rate of rehospitalization within 1 year (48.3% vs 51.5%, $P < 0.05$).

We next performed a risk stratification analysis within the group of NSAP patients. We analyzed associated signs and symptoms presented upon admission and those evolving during the course of hospitalization and their association with clinical outcomes during hospital stay and 30-days postdischarge (Table 2). Associated vomiting and hyponatremia (122.9 ± 5.1 vs 136.0 ± 4.1 meq/L in the nonhyponatremia group), upon hospital admission or occurring during hospitalization, were significantly more prevalent among patients who died during their hospital stay or during the 30-day period after discharge (for vomiting 16.9% vs 5.6% and for hyponatremia 8.5% vs 3.0% among patients who died during hospitalization, $P < 0.05$ for both comparisons). Vomiting and hyponatremia during hospitalization were also more prevalent among patients who died during the 30-day period after discharge (for vomiting 13.6% vs 5.7% and for hyponatremia 8.5% vs 2.9%, $P < 0.05$ for both comparisons). Associated bowel obstruction was found to be more prevalent among NSAP patients who died during the 30-day period after discharge (6.8% vs 1.7%, $P < 0.05$) but this was not the case for patients who died during their hospital stay. Hyponatremia was independently associated with increased mortality risk in both groups. Yet, this effect was significantly higher in the NSAP compared to the control group (HR = 2.8 vs 1.6, respectively [$P < 0.05$]).

Among the 2144 patients in the NSAP group, 119 had a documented diagnosis of vomiting (5.5%), 68 (3.2%) had a diagnosis of hyponatremia, and 7 patients (0.03%) had the combination of vomiting and hyponatremia. In a multivariable logistic regression model including vomiting and hyponatremia, both were significant predictors of 30 days mortality with respective hazards ratio of 2.8 and 2.1 ($P < 0.005$ for both), suggesting that these are 2 independent risk factors.

Signs and symptoms found to be more prevalent among patients who were rehospitalized during the period of 30-days post discharge were dyspnea (4.6% vs 2.4%), hyponatremia (5.0% vs 2.6%), anemia (6.8% vs 4.4%), $P < 0.05$ for all comparisons.

DISCUSSION

Better characterization and prognostication of patients hospitalized due to nonsurgical abdominal pain could improve treatment in such patients. In the community setting, a recent literature review by Viniol et al concluded that there is much need for better guidelines and decision-support tools for such patients in the primary care.[7] Moreover, during the triage sequence in the emergency department, physicians are used to applying risk-stratification calculations in order to assess, both short- and long-term prognosis, according to their working diagnosis. For example, Dipaola et al discussed the importance of risk stratification of patients presenting with syncope to the ED,[8] Kang et al present a risk stratification model for cases of acute pyelonephritis in order to indicate cases necessitating hospital admission,[9] Spinar et al,[10] and others, further improved our knowledge regarding the appropriate risk stratification process of patients with acute heart failure.

In a large epidemiological study, Murata and colleagues[2] showed that the etiology of acute abdominal pain in patients

TABLE 1. Characteristics of Patients Admitted Due to NSAP vs Matched Controls (Matched on the Charlson Comorbidity Index at Admission)

	Abdominal Pain (N = 2144)	No Abdominal Pain (N = 21,440)	*P* Value
Demographic data			
Female gender (%)	56.80%	56.80%	NS
Age (years ± SD)	64.5 ± 20.0	64.5 ± 19.5	NS
Age >65 years (%)	55.1	54.6	NS
BMI	26.7	27.6	NS
Charlson comorbidity index, age adjusted	2.95 ± 1.81	2.96 ± 1.76	NS
Associated complaints at presentation			
Diarrhea	5.3	1.25	<0.001
Constipation	2.9	0.26	<0.001
Chast pain	3.3	4.6	<0.05
Dyspnea	2.9	3.6	NS
Fever	5.3	4.5	NS
Gastrointestinal bleeding	0.79	0.51	NS
Vomiting	5.9	0.9	<0.001
Background diagnoses (%)			
Atrial fibrillation	3.6	3.8	NS
Anemia	4.2	4.4	NS
Colon cancer	0.65	0.31	<0.05
Pancreas cancer	0.56	0.11	<0.001
Metastatic cancer	0.84	0.72	NS
Congestive heart failure (CHF)	1.8	4.2	<0.001
Chronic obstructive pulmonary disease (COPD)	1	2.2	<0.001
Dementia	0.42	0.88	<0.05
Depression	1.1	0.8	NS
Diabetes mellitus	4.9	5.2	NS
Famillial mediterranean fever (FMF)	1.3	0.1	<0.001
Arteial hypertension (HTN)	10.3	8.7	<0.05
Inflammatory bowl disease (IBD)	1.2	0.3	<0.001
Ischemic heart disease (IHD)	4.3	5	NS
Chronic liver disease	2.3	1.1	<0.001
Current smoker	1.6	1.4	NS
Peptic ulcer disease	1.8	0.4	<0.001
Initial vital signs			
Systolic blood pressure (mm Hg, median)	127	130	NS
Diastolic blood pressure (mm Hg, median)	65.7	66.2	NS
Heart rate (median)	85	78	NS
Saturation (%)	96.4	96.1	NS
Initial laboratory values			
WBC	9.88	10.4	<0.05
C-reactive protein	48.7	61.8	<0.001
Amylase	68.7	73.1	NS
Lipase	46.9	61.2	<0.05
Alkaline phosphatase	119	112	<0.05
Bilirubin (total)	0.829	0.82	NS
Bilirubin (direct)	0.284	0.349	<0.05
Urea	45.3	53.9	<0.001
Creatinine	1.28	1.35	<0.05
GFR (MDRD)	56	55	<0.05
Hemoglobin (g/dL)	12.3	11.9	<0.001
LDH	294	288	<0.001
Lactate	20.2	21.5	<0.001
PH	7.37	7.36	<0.001
ALT	38.2	37.6	NS
Sodium	138	138	NS
Troponin I	0.176	0.457	<0.001
Uric acid	5.56	5.94	<0.001
Clinical outcomes			
Death during hospital stay	2.8% (59/2144)	5.5% (1186/21440)	<0.001

	Abdominal Pain (N = 2144)	No Abdominal Pain (N = 21,440)	*P* Value
Length of hospital stay	3.92 ± 8.22	6.16 ± 21.8	<0.001
30 days mortality	7.9% (170/2144)	10.4% (2239/21440)	<0.001
1 year mortality	22.5% (482/2144)	25.5% (5470/21440)	<0.05
30 days rehospitalization	23.3% (499/2144)	24.6% (5282/21440)	NS
1 year rehospitalization	48.3% (1035/2144)	51.5% (11041/21440)	<0.05

ALT = alanine transaminase, BMI = body mass index, CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, FMF = famillial mediterranean fever, HTN = hypertension, IBD = inflammatory bowl disease, IHD = ischemic heart disease, LDH = lactate dehydrogenase, NSAP = nonsurgical abdominal pain, SD = standard deviation.

presenting to the ED, varies according to their age, and that acute appendicitis was more frequent in patients aged 20 to 39 years, whereas ileus was more common in patients aged 60 to 79 years. In their study, ''intestinal infection'' was the most common etiology of acute abdominal pain in both men and women presenting to the ED. However, we did not find in the literature a risk stratification and prognostication algorithm for ''nonsurgical'' abdominal pain, in a manner similar to what has been described, for example, in ''nontraumatic'' low-back pain patients.[11]

Specifically regarding cases of abdominal pain, multiple laboratory parameters and imaging modalities can assist physicians investigating the etiology of abdominal pain. In their prospective study, Abbas and colleagues showed that a simple compilation of clinical and laboratory findings could stratify patients in the ED into low- and high-risk groups, and suggest management strategies accordingly.[12] Nevertheless, they did not consider the population of patients admitted for further investigation in nonsurgical departments, classified as NSAP, for which a risk-stratification model is still lacking. Scheinfeld and colleagues proposed to use laboratory and clinical parameters in abdominal pain patients to assess the need for CT scan.[13] They did not, however, include elderly patients, in which acute abdominal pain have different etiologies.

The authors of the present study launched this wide-scale analysis in order to evaluate the overall prognosis of patients hospitalized due to NSAP. We found that as a whole, this group of patients has a better prognosis when compared to the overall population hospitalized in general medicine departments. This finding is true even after controlling for age, gender, and

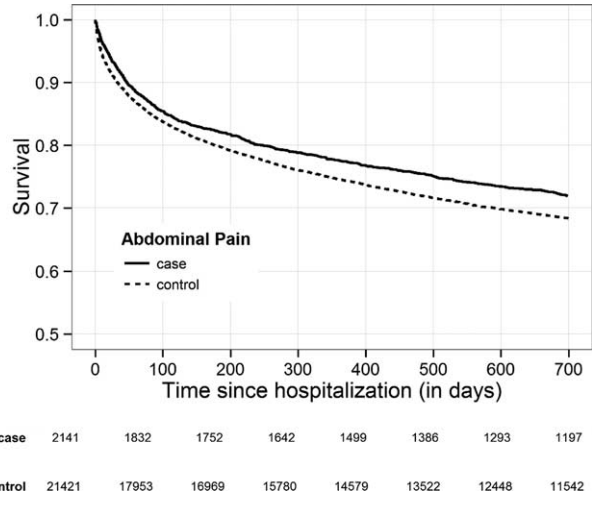

FIGURE 1. Kaplan–Meier survival curve of survival of both study groups.

Charlson comorbidity index. Several potential explanations exist for our findings: (a) abdominal pain that is not associated with an anatomic anomaly (such as volvulus or overt intestinal obstruction) is often due to functional derangements of intestinal motility, for which in-hospital investigation is unnecessary and are better suited to elective outpatient investigation, such as in the case of irritable bowel syndrome; (b) abdominal pain that is not associated with intra-abdominal inflammation (after excluding signs of peritoneal irritation) are most probably associated with an extra-abdominal inflammatory disease which harbors a lesser degree of risk for patients when compared to clear-cut inflammatory diseases such as pneumonia or urinary tract infections. These results may be explained by the fact that substantial amount of patients with NSAP may be classified as irritable bowel disease. In the work of Hollowell et al, it was estimated that about 11.3 visits per 1000 annual ambulatory physician visits in the United States are due to irritable bowel syndrome, of which 1% were emergency department visits.[14]

Regarding the results of our in-group analysis of NSAP patients, we found that both hyponatremia and vomiting were significantly more prevalent among NSAP patients who died during and shortly after hospitalization. The association of hyponatremia with mortality has been described previously in several studies. The mere presence of serum sodium concentration <135 meq/L has been associated with increased mortality risk in the general population.[15] Moreover, similar findings were documented in specific populations such as hospitalized patients[16] and in patients with chronic kidney disease.[17] In the prospective work of Wannamethee et al mild hyponatremia including low-normal values were associated with increased in all-cause mortality in elderly men followed for an average period of 11 years. The authors concluded that in elderly men, even low-normal levels (of 136 to 138 meq/L) may mark an increased risk of both total mortality and cardiovascular risk, and are definitely not a benign finding.[18] Saepudin et al have found that in patients hospitalized with heart failure, hyponatremia during hospitalization was associated with longer hospital stay and mortality during hospitalization compared to patients with normal plasma sodium concentration. The study revealed that hyponatremia is a surrogate marker for patients with more severe disease and therefore of worse prognosis, in terms of mortality during hospital stay.[19]

Vomiting is a nonspecific medical complaint which may be associated with different clinical scenarios, both related and unrelated to the gastrointestinal tract. Hyponatremia might be the result of excessive vomiting by virtue of both fluids and electrolytes loss, as well as in association with metabolic alkalosis.[20,21] In a prospective multicenter study of elderly patients with profound hyponatremia, vomiting was abundant in 30% of this population.[22] Moreover, among the range of symptoms characterizing patients with hyponatremia, nausea

TABLE 2. Associated Signs and Symptoms Upon Admission and During the Course of Hospitalization With Clinical Outcomes of NSAP Patients During Hospital Stay and 30-Days PostDischarge

	Death During Hospitalization			30-d Postdischarge Mortality			30-d Postdischarge Rehospitalization		
	No (n = 2085)	Yes (n = 59)	*P* Value	No (n = 1974)	Yes (n = 170)	*P* Value	No	Yes	*P* Value
Signs and symptoms first reported upon hospital admission									
Diarrhea	5.40%	0	NS	5.50%	2.40%	NS	5.80%	3.60%	NS
Constipation	2.80%	6.80%	NS	2.70%	5.30%	NS	2.70%	3.60%	NS
Chest pain	3.30%	1.70%	NS	3.50%	0.59%	<0.05	3.50%	2.60%	NS
Dyspnea	2.90%	3.40%	NS	2.70%	5.30%	NS	2.40%	4.60%	<0.05
Fever	5.20%	8.50%	NS	5.30%	5.30%	NS	5.50%	4.40%	NS
Gastrointestinal bleeding	0.77%	1.70%	NS	0.71%	1.80%	NS	0.85%	0.60%	NS
Vomiting	5.60%	16.90%	<0.05	5.20%	13.50%	<0.001	5.40%	7.40%	NS
Hyponatremia	3.00%	8.50%	< 0.05	2.90%	6.50%	< 0.05	2.60%	5.00%	< 0.05
Bowel obstruction	0.29%	1.70%	NS	0.30%	0.59%	NS	0.30%	0.40%	NS
Anemia	4.20%	5.10%	NS	4.30%	4.10%	NS	3.80%	5.80%	NS
Signs and symptoms first reported during hospital stay									
Diarrhea	6.70%	1.70%	NS	6.90%	2.90%	NS	7.20%	4.60%	< 0.05
Constipation	4.50%	6.80%	NS	4.50%	5.90%	NS	4.30%	5.60%	NS
Chest pain	3.10%	1.70%	NS	3.20%	1.18%	NS	3.50%	1.40%	< 0.05
Dyspnea	2.10%	0.00%	NS	2.10%	1.18%	NS	2.00%	2.20%	NS
Fever	4.30%	10.20%	< 0.05	4.40%	5.30%	NS	4.60%	4.00%	NS
Gastrointestinal bleeding	0.82%	3.40%	NS	0.71%	2.90%	< 0.05	0.85%	1.00%	NS
Vomiting	5.70%	13.60%	< 0.05	5.40%	11.20%	< 0.05	5.70%	6.60%	NS
Hyponatremia	2.90%	8.50%	< 0.05	2.80%	5.90%	< 0.05	2.80%	4.00%	NS
Bowel obstruction	1.70%	6.80%	< 0.05	1.60%	4.70%	< 0.05	1.80%	2.00%	NS
Anemia	5.00%	5.10%	NS	5.00%	5.30%	NS	4.40%	6.80%	< 0.05

NSAP = nonsurgical abdominal pain.

and vomiting are prevalent presenting symptoms. In fact vomiting is often the first nonspecific sign of hyponatremia.[23] An additional link between abdominal pain, hyponatremia, and poor clinical outcome could be an unrecognized adrenal crisis. In the recent review of Puar et al,[24] failure to recognize and adequately treating adrenal crisis are common. An overlooked adrenal crisis carries a poor prognosis and pathologies originating from the gastrointestinal tract are still the most frequent precipitant for an adrenal crisis.

CONCLUSION

This retrospective analysis imply that compared to patients hospitalized due to other, nonsurgical reasons, the overall prognosis of patients admitted due to NSAP is favorable. The combination of NSAP with vomiting and hyponatremia is associated with worse clinical outcomes. We suggest that these findings will be taken into consideration by both emergency and Internal Medicine physicians during the process of clinical decision making for the aforementioned patients. Triage guidelines could be drawn from our study results but should be, further enforced, by results of prospective, controlled studies.

STUDY LIMITATIONS

Our study has several limitations: since it is a retrospective analysis, further prospective studies should investigate the possible causality between certain indices upon admission and future prognosis in the NSAP patient population. Additionally, we did not include all the diagnostic modalities used, nor treatments applied by the admitting physicians at the time of admission. We do not know which imaging modalities were utilized and to what extent their results influenced the decision whether to hospitalize some patients to surgical departments or other, nonsurgical departments.

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