ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2019 October 27; 11(10): 701-724

Published by Baishideng Publishing Group Inc

World Journal of Hepatology

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Monthly Volume 11 Number 10 October 27, 2019

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NAME OF JOURNAL
World Journal of Hepatology

ISSN
ISSN 1948-5182 (online)

LAUNCH DATE
October 31, 2009

FREQUENCY
Monthly

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World Journal of Hepatology

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World J Hepatol 2019 October 27; 11(10): 701-709

DOI: 10.4254/wjh.v11.i10.701

ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Impact on 30-d readmissions for cirrhotic patients with ascites after an educational intervention: A pilot study

Nicholas Lim, Otto Sanchez, Andrew Olson

ORCID number: Nicholas Lim (0000-0001-9740-8923); Otto Sanchez (0000-0003-0256-8065); Andrew Olson (0000-0002-7226-5783).

Author contributions: Lim N and Olson A designed the study; Lim N gathered the data; Sanchez O compiled figures and tables, and performed statistical analysis; Lim N and Olson A wrote the initial and final drafts of the manuscript; All authors have read and approved the final manuscript.

Institutional review board statement: This study was conducted with the approval of the institutional review board at the University of Minnesota, No. 1601S83245.

Informed consent statement: Due to its retrospective nature, informed consent was not required for this study.

Conflict-of-interest statement: The authors have no financial disclosures or conflicts-of-interest to declare.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at nlim@umn.edu. Informed consent was not required due to the retrospective nature of this study but all presented data are anonymized and risk of identification is low.

STROBE statement: The guidelines of the STROBE Statement have been adopted.

Open-Access: This article is an

Nicholas Lim, Division of Gastroenterology, Hepatology and Nutrition, University of Minnesota, Minneapolis, MN 55455, United States

Otto Sanchez, Division of Renal Diseases and Hypertension, University of Minnesota, Minneapolis, MN 55455, United States

Andrew Olson, Division of General Internal Medicine, University of Minnesota, Minneapolis, MN 55455, United States

Corresponding author: Nicholas Lim, MD, Assistant Professor, Division of Gastroenterology, Hepatology and Nutrition, University of Minnesota, 420 Delaware St SE, MMC 36, Minneapolis, MN 55455, United States. nlim@umn.edu
Telephone: +1-6-126258999

Abstract

BACKGROUND

A low proportion of patients admitted to hospital with cirrhosis receive quality care with timely paracentesis an important target for improvement. We hypothesized that a medical educational intervention, delivered to medical residents caring for patients with cirrhosis, would improve quality of care.

AIM

To determine if an educational intervention can improve quality of care in cirrhotic patients admitted to hospital with ascites.

METHODS

We performed a pilot prospective cohort study with time-based randomization over six months at a large teaching hospital. Residents rotating on hospital medicine teams received an educational intervention while residents rotating on hospital medicine teams on alternate months comprised the control group. The primary outcome was provision of quality care- defined as adherence to all quality-based indicators derived from evidence-based practice guidelines- in admissions for patients with cirrhosis and ascites. Patient clinical outcomes- including length of hospital stay (LOS); 30-d readmission; in-hospital mortality and overall mortality- and resident educational outcomes were also evaluated.

RESULTS

Eighty-five admissions (60 unique patients) met inclusion criteria over the study period-46 admissions in the intervention group and 39 admissions in the control group. Thirty-seven admissions were female patients, and 44 admissions were for alcoholic liver disease. Mean model for end-stage liver disease (MELD)-Na score

Manuscript source: Unsolicited manuscript

Received: June 17, 2019
Peer-review started: June 18, 2019
First decision: July 17, 2019
Revised: September 23, 2019
Accepted: October 2, 2019
Article in press: October 2, 2019
Published online: October 27, 2019

P-Reviewer: Soldera T, Streba LAM
S-Editor: Ma YJ
L-Editor: A
E-Editor: Ma YJ

at admission was 25.8. Forty-seven (55.3%) admissions received quality care. There was no difference in the provision of quality care (56.41% *vs* 54.35%, P = 0.9) between the two groups. 30-d readmission was lower in the intervention group (35% *vs* 52.78%, P = 0.1) and after correction for age, gender and MELD-Na score [RR = 0.62 (0.39, 1.00), P = 0.05]. No significant differences were seen for LOS, complications, in-hospital mortality or overall mortality between the two groups. Resident medical knowledge and self-efficacy with paracentesis improved after the educational intervention.

CONCLUSION
Medical education has the potential to improve clinical outcomes in patients admitted to hospital with cirrhosis and ascites.

Key words: Cirrhosis; Education; Paracentesis; Quality

Core tip: Quality care remains relatively low in patients admitted to hospital with cirrhosis. Diagnostic paracentesis in patients with ascites has been identified as a target to improve quality in these patients. We developed and administered an educational intervention focused on paracentesis to medical residents caring for patients with cirrhosis using time-based randomization. After adjustment for model for end-stage liver disease-Na score, age and gender, patients in the intervention group had reduced 30-d readmissions. As health care costs rise, our results justify further study into the use of medical education to improve the delivery of quality care in patients with cirrhosis.

Citation: Lim N, Sanchez O, Olson A. Impact on 30-d readmissions for cirrhotic patients with ascites after an educational intervention: A pilot study. *World J Hepatol* 2019; 11(10): 701-709
URL: https://www.wjgnet.com/1948-5182/full/v11/i10/701.htm
DOI: https://dx.doi.org/10.4254/wjh.v11.i10.701

INTRODUCTION

The prevalence of cirrhosis is increasing annually and chronic liver disease is currently the twelfth leading cause of death in the United States[1-3]. As expected, this has led to an increase in hospitalizations in cirrhotic patients for all diagnoses, including hepatic encephalopathy, sepsis and renal failure[4,5].

There is an increasing focus on the delivery of quality care in medicine, and hepatology in particular, due to rising health care costs and the use of alternative payment models in health care[6]. In 2010, a set of quality indicators for patients with cirrhosis were identified by an expert panel with the intention of setting a platform for the delivery of quality care[7]. Recent studies have examined the quality of care provided to hospitalized cirrhotic patients and concluded that the minority of patients receive high quality care[8-11].

It is therefore important to develop processes that can improve the quality of care delivered to cirrhotic patients admitted to the hospital. One recent study showed that co-management between hepatologists and hospitalists increased the quality of care for patients admitted with spontaneous bacterial peritonitis (SBP) when compared to a standard generalist-consultant model[12]. Another study looked at the development of an order set in the electronic health record to improve clinical outcomes in the care of patients hospitalized with variceal bleeding and demonstrated improvements in the use and time to administration of antibiotics, a key quality indicator[13].

In a previous study, we identified timely paracentesis as an area for improvement for physicians admitting cirrhotic patients with ascites to the hospital[11]. A multi-hospital discharge database study showed that early paracentesis has been shown to be associated with improved mortality in patients admitted to the hospital with ascites[14,15].

The objective of this study was to evaluate how the use of medical education impacts on the provision of quality of care in cirrhotic patients admitted to hospital with ascites.

MATERIALS AND METHODS

The University of Minnesota Medical Center (UMMC) is a tertiary care medical center with a high-volume liver transplant program. Similar to other high-volume transplant centers in the United States, patients with cirrhosis are admitted to either a hospital medicine team, staffed by a hospitalist with or without internal medicine residents, or the intensive care unit. This study was conducted with approval of the institutional review board at University of Minnesota. All authors had access to the study data and have reviewed and approved the final manuscript.

The University of Minnesota internal medicine and internal medicine-pediatrics residency programs comprise 42 residents per year. Residents alternate between inpatient and outpatient/elective rotations every 4 wk at three different teaching hospitals.

We performed a pilot prospective cohort study with time-based randomization over six months at one of the teaching hospitals (UMMC). Residents rotating on hospital medicine teams received an educational intervention (see below) while residents rotating on hospital medicine teams on alternate months comprised the control group.

The intervention was an educational session occurring at the beginning of the 4-wk rotation. The educational session comprised a 15-min tutorial and a 45-min practical training session. The didactic tutorial was delivered by an attending hepatologist and/or hospitalist and described indications, contraindications, and mechanics of paracentesis in addition to other aspects of care for patients with ascites. The practical training session involved hands-on teaching of ultrasound-guided paracentesis using a paracentesis training model. Residents in the intervention group also received a pocket-sized card with information on paracentesis and care for patients with ascites at the end of the educational session.

Residents in both groups completed a vignette-based medical knowledge assessment about caring for patients with ascites, as well as a survey regarding self-efficacy in paracentesis and caring for patients with ascites at the beginning of each rotation (Supplement 1). Residents in the intervention group completed another medical knowledge assessment and self-efficacy survey at the end of the educational session. A final self-efficacy survey was completed by residents in the intervention group 6 months after delivery of the educational intervention.

Patient data was then retrospectively collected on admissions for patients cared for by internal medicine residents on hospital medicine teams during the study period. Patients were included for analysis if they were admitted to the UMMC with cirrhosis and ascites to the hospitalist service *via* the UMMC emergency room. Patients were allocated to the intervention group if the residents caring for them had received the educational intervention at the beginning of their hospital medicine rotation. The control group comprised all other patients eligible for analysis.

Patients were excluded from analysis if they were not cared for by residents; if they were younger than 18 years old; had been transferred from another institution; if they were not admitted to the hospitalist service; if there was a concurrent diagnosis of hepatocellular carcinoma and/or if they had a "do not resuscitate" or "do not intubate" order that may have reduced the likelihood of invasive care measures.

Outcomes

The primary outcome was delivery of quality care. Quality care was defined as adherence to all quality indicators for ascites derived from society-based clinical practice guidelines[11] (Table 1).

Secondary outcomes included length of hospital stay; complications; 30-d readmission; in-hospital mortality; 30-d mortality and overall mortality.

A complication was defined as a new, distinct clinical problem contributing towards length of stay. Complications included, but were not limited to, gastrointestinal bleeding; hepatic encephalopathy; acute kidney injury and sepsis. Complications were designated as "mild" *i.e.*, not life-threatening, "moderate" *i.e.*, possibly life-threatening or "severe" *i.e.*, life-threatening.

Educational outcomes were resident knowledge on paracentesis and care of patients with ascites, and resident self-efficacy in paracentesis and caring for patients with ascites. Data on resident medical knowledge and self-efficacy were obtained before, after and 6-mo after the intervention as appropriate. Data on resident medical knowledge and paracentesis self-efficacy were obtained at the beginning of each 4-wk rotation in the control group.

Statistical analysis

Continuous variables are presented as mean (SD) and categorical variables as percentages as appropriate. Differences between groups were assessed using

Table 1 Quality indicators for ascites

Refractory ascites
Diagnostic paracentesis in a timely manner
Aspirated fluid sent for cell count, differential and culture
Management with diuretics and sodium restriction in patients with normal renal function

independent student's *t*-test and Chi-square tests for continuous and categorical variables, respectively. Relative risks (RR) for clinical outcomes were adjusted for age, sex and the presence at admission of coronary artery disease (CAD), model for end-stage liver disease score (MELD score) and if hepatology consult was requested or not. Statistical significance was set at a *P* value of 0.05. SAS version 9.3 (SAS Institute Inc., Cary, NC) was used for all statistical analysis.

RESULTS

Demographics

Over the six-month study period, there were 85 admissions (60 individual patients) satisfying the inclusion criteria: 46 admissions in the intervention group and 39 admissions in the control group. 37 admissions (43.5%) were female. The mean (SD) age of the cohort was 53.5 (11.2) years. With regard to etiology of liver disease, 44 admissions (51.8%) were for alcoholic cirrhosis. Mean (SD) MELD-Na score of the cohort was 25.8 (7.04). There were no differences observed between the intervention and control groups for gender, age, MELD-Na score at admission, etiology of liver disease or the presence of coronary artery disease (CAD), diabetes, HIV or portal vein thrombosis. There was a significantly higher proportion of admissions with chronic kidney disease (CKD) in the intervention arm compared to the control arm (39 *vs* 25 admissions, $P = 0.03$). A hepatology consult was obtained in 30 admissions in the intervention group compared to 22 admissions in the control group (65.2% *vs* 56.4%, $P = 0.4$) (Table 2). No significant differences were observed between the two groups with regard to laboratory values at the time of admission (Supplement 2).

Primary outcome

Forty-seven (52.3%) admissions met criteria (adherence to 3/3 quality indicators) for the primary outcome of quality care. For the primary outcome, no significant difference was observed between the intervention group and the control group (25/46 admissions (54.4%) *vs* 22/39 admissions (56.4%), $P = 0.9$). Of the 38 admissions not meeting criteria for quality care, 16 (18.8%) admissions adhered to 0/3 quality indicators; 12 (14.1%) admissions adhered to 1/3 quality indicators, and 10 (11.8%) admissions adhered to 2/3 quality indicators (Table 3).

With regard to adherence to specific quality indicators, timely paracentesis was performed in 49/85 (57.6%) admissions; appropriate testing was sent on ascitic fluid in 66/85 (77.6%) admissions, and management with sodium restriction and diuretics (when appropriate) occurred in 57/85 (67%) admissions.

In the intervention group, timely diagnostic paracentesis was performed in 24/46 (52%) admissions; appropriate studies were ordered on ascitic fluid in 31/46 (67%) admissions and appropriate management of ascites occurred in 26/46 (56.5%) admissions. In the control group, timely diagnostic paracentesis was performed in 25/39 (64%) admission; appropriate ascitic fluid studies ordered in 35/39 (90%) admissions and appropriate management of ascites in 31/39 (79%) admissions.

Secondary outcomes

Length of stay: The mean (SD) length of stay did not differ between the intervention and control groups [8.95 (12.8) *vs* 11.1 (10.9) d, $P = 0.4$] (Table 3). However, on multivariate analysis-after adjustment for age, gender, presence of CKD, MELD-Na score at admission and hepatology consult- the relative risk for a length of hospital stay of > 6 d was 10% higher in the intervention group (RR = 1.10, 95%CI: 0.69-1.74, $P = 0.1$) (Table 4).

Complications: Twenty-one (45.7%) admissions in the intervention group encountered complications: 5 admissions with mild/non-life-threatening complications; 5 admissions with moderate/possibly life-threatening complications and 7

Table 2 Baseline characteristics, *n* (%)

Groups	Control (*n* = 39)	Intervention (*n* = 46)	*P* value
Female	18 (46.2)	19 (41.3)	0.7
Age, yr	51.9 (11.4)	54.9 (10.9)	0.2
Hepatology consult	22 (56.41)	30 (65.22)	0.4
MELD-Na score	25.5 (6.2)	26.1 (7.7)	0.7
Comorbidities			
CAD	3 (7.69)	4 (8.7)	0.9
CKD	25 (64.1)	39 (84.78)	0.03
DM	11 (28.21)	17 (36.96)	0.4
HD	11 (28.21)	16 (34.78)	0.5
HIV	3 (7.69)	0 (0)	0.06
PVT	5 (12.82)	6 (13.04)	1
Etiology of cirrhosis			0.3
ETOH	23 (58.97)	21 (45.65)	
Hepatitis C	1 (2.56)	5 (10.87)	
ETOH/Hep C	3 (7.69)	2 (4.35)	
Hepatitis B	3 (7.69)	1 (2.17)	
NASH	4 (10.26)	8 (17.39)	
Other	5 (12.82)	9 (19.57)	

MELD-Na: Model of end-stage liver disease-sodium; CAD: Coronary artery disease; CKD: Chronic kidney disease; DM: Diabetes mellitus; HD: Hemodialysis; HIV: Human immunodeficiency virus; PVT: Portal vein thrombosis; ETOH: Alcohol; NASH: Non-alcoholic steatohepatitis.

admissions with severe/life-threatening complications. 17 (43.6%) admissions in the control group had complications: 3 admissions with mild complications; 8 admissions with moderate complications and 10 admissions with severe complications. No difference was observed in the proportion of complications seen in the intervention group compared to the control group (45.7% *vs* 43.6%, $P = 0.9$) (Table 3).

30-d readmissions: Re-admission to hospital within 30 days of discharge was seen in 14 admissions in the intervention group compared to 19 admissions in the control group (35% *vs* 52.8%, $P = 0.1$) (Table 3). The relative risk of 30-day admissions was 38% lower in the intervention group after adjustment for age, gender, CKD, MELD-Na score and hepatology consult (RR = 0.62, 95%CI: 0.39-1.00, $P = 0.05$) (Table 4).

Mortality: Three admissions in the intervention group concluded with in-hospital death compared to 3 admissions in the control group (13% *vs* 7.7%, $P = 0.4$). 3 admissions in the intervention group died within 30 d of admission to hospital compared to 4 admissions in the control group (7.5% *vs* 11.1%, $P = 0.6$). With regard to overall mortality, there were 15 deaths at the end of follow-up in the intervention group compared to 12 deaths in the control group (32.6% *vs* 30.8%, $P = 0.9$) (Table 3).

Educational outcomes

Overall, 46 residents participated in the study. The composition of resident teams caring for patients was identical between groups. Educational outcomes have been reported in full elsewhere.

Overall mean resident score in the medical knowledge assessment on paracentesis and care of patients with ascites increased from 50% pre-intervention to 59.2% post-intervention ($P = 0.07$). Satisfaction with paracentesis training improved from 19.4% pre-intervention to 28.6% immediately post-intervention and 66.7% six-months post-intervention ($P < 0.05$). Mean self-efficacy score in performing paracentesis with indirect supervision increased from 2.5/4 (on a 4-point Likert scale) pre-intervention to 2.9/4 immediately post-intervention and 3.4/4 six-months post-intervention ($P = 0.08$).

DISCUSSION

Quality care remains suboptimal for patients admitted to hospital with cirrhosis and

Table 3 Adherence to quality care and clinical outcomes, *n* (%)

Groups	Control (*n* = 39)	Intervention (*n* = 46)	*P* value
Quality care	22 (56.41)	25 (54.35)	0.9
Length of stay, d	8.95 (12.8)	11.1 (10.9)	0.4
Complications	17 (43.59)	21 (45.65)	0.9
30-d readmission	19 (52.78)	14 (35)	0.1
In-hospital mortality	3 (7.69)	6 (13.04)	0.4
30-d mortality	4 (11.11)	3 (7.5)	0.6
Total mortality	12 (30.77)	15 (32.61)	0.9

ascites. In our study, 52.3% of admissions received quality care, which is consistent with figures reported in other studies[8-11]. In our cohort, only 61.2% of admissions received a hepatology consult which may explain the relatively low proportion of patients receiving quality care. One study showed reduced inpatient mortality, hospital length of stay and readmission rates in patients with cirrhosis who received gastroenterology consult when admitted to hospital in VA system[16].

We did not find any significant difference between the intervention and control groups with regard to the primary outcome of quality care. The lack of a significant difference in the primary outcome may be related to the content of the educational intervention, which focused largely on the practical aspects of paracentesis. Analysis of adherence to individual quality indicators showed that diagnostic paracentesis was performed in a timely manner in only 57.6% of admissions. Whilst medical knowledge improved after the educational intervention, this difference was not statistically significant, and increased focus on the pedagogical aspect of the intervention could improve this figure. This quality indicator remains an ideal target for improvement as two recent studies have demonstrated a relationship between inpatient mortality and timely paracentesis[14,15].

It is also possible that the lack of involvement of the night float admitting residents contributed to the negative primary outcome. Our center uses a night float system when admitting patients to the hospitalist service after hours, a system that is commonplace in hospital medicine nowadays. The rotating night float resident was not captured in the educational intervention but the patients they admitted during intervention months would have been counted towards the intervention group. On review, 15 admissions in the intervention group were admitted by the night float resident. This issue may be addressed in the future with the use of online learning modules accessible to all at any time of day. Similar initiatives have been used to deliver educational material in laparoscopic cholecystectomy techniques to surgical trainees and in the education of all trainees in chronic kidney disease[17,18].

We did find a trend towards reduced 30-d readmission rates in the intervention group before and after adjustment for differences in age, gender, MELD-Na score and CKD with the control group. Whilst quality of care would not explain this finding, it is possible that our educational intervention altered behavior in another way or engendered a heightened awareness of the complexity of patients with cirrhosis. It is also worth noting that the rate of 30-d readmissions in the control group was relatively high compared to previous studies, likely reflecting our sicker study population[19,20]. Reducing 30-d readmissions has significant financial implications for hospitals and payers as admissions to hospital for cirrhosis-related complications increase, and as health care costs in the United States continue to rise: chronic liver disease accounted for over $3.3 billion in health care expenditure in 2012[5,21].

Our study is the first to evaluate if medical education can improve quality care in patients admitted to hospital with cirrhosis and ascites. Previous studies have used checklists and order sets to improve quality in patients with cirrhosis[13,19,22]. Medical education has been shown to reduce surgical complications by orthopedics residents; increase screening rates for hepatitis C by primary care residents and reduce inappropriate ordering of echocardiograms by internal medicine residents[23-25]. We noted improved self-efficacy with regard to paracentesis in residents after the educational intervention. Self-efficacy with paracentesis also persisted over time demonstrating the durability of our educational intervention.

Previous studies have measured the proportion of adherence to quality indicators when evaluating delivery of care in patients with cirrhosis and have failed to demonstrate an improvement in mortality[8-10]. Our study differs from previous work by using an all-or-nothing definition of quality care with regard to adherence to quality indicators. Furthermore, we evaluated patient admissions, as opposed to

Table 4 Adjusted relative risk for clinical outcomes related to intervention group

	Intervention [RR (95%CI)]	*P* value
Length of stay > 6 d	1.10 (0.69, 1.74)	0.1
Complications	0.93 (0.58, 1.50)	0.8
30-d readmission	0.62 (0.39, 1.00)	0.05
30-d mortality	0.95 (0.30, 2.99)	0.7
Total mortality	1.07 (0.54, 2.13)	0.8

individual patients, as admissions were viewed as opportunities for quality care.

A disconnect currently exists between medical education and clinical outcomes. Educational research has traditionally focused purely on learner outcomes but should be focusing on the synchronization of learning and clinical outcomes. Patients with cirrhosis are an ideal population to expand this research due to their limited heterogeneity. Furthermore, SBP could be a key disease for study due to its clear diagnostic criteria and well-validated quality measures[26]. This would promote study in residency programs across institutions allowing mutual learning and improvements in clinical care. One study has shown that maternal complications in obstetrics patients were associated with the obstetrician's residency program[27]. Improving residency education therefore has the potential to affect quality of care and patient outcomes on thousands of patients in the future.

Our study has several limitations. First, this is a single center study so certain practices and culture at our institution, *e.g.*, hospital-based model of inpatient care, may not be generalizable to other medical centers. The pilot nature of our study meant that it was underpowered to fully evaluate differences in readmissions, mortality, complications and transfer to the ICU. A multi-center study would address both issues. Third, our intervention was directed at medical residents. The applicability of our medical educational intervention to medical students, advanced practice providers and staff physicians is unknown. Fourth, it is not possible to capture true readmission rates as patients may re-present to different hospitals. To mitigate this, we only included admissions presenting *via* UMMC ER, and excluded those transferred from other institutions. Finally, the nature of residency training made it impossible to prevent cross-fertilization of knowledge between the intervention and control groups despite best efforts. The impact of this however would have been softened by the rotation of residents between the three teaching hospitals affiliated with the University of Minnesota for their inpatient rotations.

In summary, a gap remains in the provision of quality care for patients admitted to hospital with decompensated cirrhosis. The use of medical education to improve quality care in this population remains a novel and relatively unproven idea with the potential to improve clinical outcomes particularly hospital readmission rates. Given the low cost and reproducible nature of our intervention, a larger scale study is justified particularly as medical education research transitions towards evaluating patient-oriented outcomes.

ARTICLE HIGHLIGHTS

Research background

The prevalence of cirrhosis in the United States is increasing with an increasing burden placed on the health care system. In 2010, a set of quality indicators were developed to provide a framework for the delivery of quality care in patients with cirrhosis. Despite this, the proportion of patients with cirrhosis receiving quality care remains relatively modest. Timely diagnostic paracentesis has been shown to be a quality indicator that is repeatedly missed in patients with cirrhosis admitted to hospital. Previous studies have shown that mandatory gastroenterology consultation, the use of standardized order sets and utilization of the electronic health record can improve quality care in patients with cirrhosis. To date, no studies have looked at the use of medical education to improve the quality of care provided to patients with cirrhosis.

Research motivation

Medical education has traditionally focused on learner outcomes. We developed an educational intervention delivered to medical residents with the intention of demonstrating that medical education could improve clinical outcomes. If proven, medical education could be a cheap and easily reproducible tool to improve quality care and other clinical outcomes in patients with cirrhosis. This is particularly relevant at a time when health care costs are rising in the United States.

Research objectives
Our main objective was to determine if an educational intervention can improve quality of care in cirrhotic patients admitted to hospital with ascites. Achieving this objective would provide one tool in addressing the deficit in quality care provided to patients with cirrhosis and stimulate further study into the use of medical education to do so.

Research methods
We conducted a pilot prospective cohort study using time-based randomization. An educational intervention was delivered to medical residents caring for patients with cirrhosis in the hospital. The control group comprised medical residents on alternate months who did not receive the educational intervention. Quality care- defined as complete adherence to all evidence-based quality indicators- was compared between the two groups. Clinical outcomes including complications, transfer to the intensive care unit, length of hospital stay, 30-d readmission and inpatient mortality were also compared.

Research results
We found that there remains a deficit in the provision of quality care in patients admitted to the cirrhosis with ascites. We found no difference in quality care between the two groups. We did find a lower rate of 30-d readmission in the intervention group that persisted after adjustment for age, gender and MELD-Na score.

Research conclusions
In this pilot study, although provision of quality care was not different between the intervention and control group, there was a reduction in 30-d readmission seen in the intervention group. There remains a deficit in quality care provided to patients with cirrhosis but the use of medical education shows potential as a cheap, effective tool to improve clinical outcomes in this population.

Research perspectives
Medical education has the potential to improve clinical outcomes in patients admitted to hospital with cirrhosis and ascites. Further refinement of our educational intervention implemented over a longer period of time may demonstrate sustained improvements in clinical outcomes in this population. Future research should look at the use of medical education to improve clinical outcomes in other patient populations such as heart failure and chronic kidney disease.

ACKNOWLEDGEMENTS

We would like to thank Gretchen Sieger of the Clinical and Translational Science Institute at the University of Minnesota for her invaluable help with data collection and organization.

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World Journal of Hepatology

Submit a Manuscript: https://www.f6publishing.com

World J Hepatol 2019 October 27; 11(10): 710-718

DOI: 10.4254/wjh.v11.i10.710

ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Observational Study

Characterization of patients with both alcoholic and nonalcoholic fatty liver disease in a large United States cohort

George Khoudari, Amandeep Singh, Mazen Noureddin, Danielle Fritze, Rocio Lopez, Imad Asaad, Eric Lawitz, Fred Poordad, Kris V Kowdley, Naim Alkhouri

ORCID number: George Khoudari (0000-0002-9570-4937); Amandeep Singh (0000-0001-8581-1408); Mazen Noureddin (0000-0003-2127-2040); Danielle Fritze (0000-0002-1950-2196); Rocio Lopez (0000-0002-4319-420X); Imad Asaad (0000-0002-0648-6625); Eric Lawitz (0000-0002-4234-224X); Fred Poordad (0000-0002-1503-1569); Naim Alkhouri (0000-0001-9872-2391).

Author contributions: All authors have contributed to this manuscript and have agreed on the content; Alkhoury N, Fritze D, and Noureddin M were involved in the study design; Khoudari G, Alkhoury N, and Singh A were involved with data analysis; Lopez R provided statistical support; Khoudari G, Kowdley K V, Singh A, Poordad F, Lawitz E, and Asaad I were involved with data interpretation, drafting and revising the work; All authors provided approval for the final version to be published.

Institutional review board statement: NHANES was approved by the Institutional Review Board at the Center for Disease Control and Prevention. This study does not require IRB approval.

Informed consent statement: Informed consent was obtained from all participants.

Conflict-of-interest statement: All authors have no conflict of interest and nothing to disclose.

George Khoudari, Department of Hospital Medicine, Cleveland Clinic Foundation, Cleveland, OH 44195, United States

Amandeep Singh, Department of Gastroenterology and Hepatology, Cleveland Clinic, Cleveland, OH 44195, United States

Mazen Noureddin, Department of Gastroenterology and Hepatology, Cedars Sinai Medical Center, Los Angeles, CA 90048, United States

Danielle Fritze, Department of General Surgery, Texas Liver Institute and University of Texas Health, San Antonio, TX 78215, United States

Rocio Lopez, Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH 44195, United States

Imad Asaad, Department of Gastroenterology, Metro Health System, Cleveland, OH 44109, United States

Eric Lawitz, Fred Poordad, Naim Alkhouri, Texas Liver Institute and University of Texas Health, San Antonio, TX 78215, United States

Kris V Kowdley, Swedish Liver Care Network, Swedish Medical Center, Seattle, WA 98122, United States

Corresponding author: George Khoudari, MD, Associate Professor, Department of Hospital Medicine, Cleveland Clinic Foundation, 29401 Hummingbird Cir, Westlake, Cleveland, OH 44195, United States. gkhoudary@gmail.com
Telephone: +1-909-5382118

Abstract

BACKGROUND

Nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the metabolic syndrome (MetS) and is characterized by steatosis in the absence of significant alcohol consumption. However, MetS and significant alcohol intake coexist in certain individuals which may lead to the development of BAFLD.

AIM

To assess the clinical characteristics of patients with both alcoholic and NAFLD (BAFLD) in a large cohort in the United States.

METHODS

Manuscript source: Unsolicited manuscript

Received: May 13, 2019
Peer-review started: May 14, 2019
First decision: June 13, 2019
Revised: August 3, 2019
Accepted: October 15, 2019
Article in press: October 15, 2019
Published online: October 27, 2019

P-Reviewer: Grgurevic I, Jamali R, Xin YN
S-Editor: Ma YJ
L-Editor: A
E-Editor: Ma YJ

Adults from the National Health and Nutrition Examination Survey between 2003-2014 were included. NAFLD was diagnosed based on elevated alanine aminotransferase (ALT) and being overweight or obese in the absence of other liver diseases. BAFLD patients met the criteria for NAFLD but also had either MetS or type 2 diabetes and consumed excessive amounts of alcohol. Univariable and multivariable analysis were performed to assess differences between NAFLD and BAFLD and to compare severity based on a validated fibrosis score (FIB4 index).

RESULTS

The prevalence of NAFLD was at 25.9% (95%CI; 25.1-26.8) and that of BAFLD was 0.84% (0.67, 1.02) which corresponds to an estimated 1.24 million Americans affected by BAFLD. Compared to NAFLD, patients with BAFLD were more likely to be male, smokers, have higher ALT, aspartate aminotransferase, triglycerides, and lower platelets; $P < 0.01$ for all. More importantly, after adjusting for MetS components, BAFLD patients were significantly more likely to have advanced fibrosis [adjusted OR (95%CI) based on FIB4 index > 2.67 was 3.2 (1.4, 7.0), $P = 0.004$].

CONCLUSION

A significant percentage of the American general population is afflicted by BAFLD and these patients tend to have more advanced liver fibrosis.

Key words: Non-alcoholic fatty liver disease; Alcoholic liver disease; Fatty liver disease

Core tip: Using the National Health and Nutrition Examination Survey dataset, we studied a new classification of fatty liver disease that we believe is due to risk factors for both non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease occurring in the same individual. We propose to call this entity Both Alcoholic and NAFLD (BAFLD). As most of the risk factors that lead to BAFLD are potentially modifiable, understanding their reciprocal association and combined effect on the liver may aid in understanding, treating, and preventing BAFLD.

Citation: Khoudari G, Singh A, Noureddin M, Fritze D, Lopez R, Asaad I, Lawitz E, Poordad F, Kowdley KV, Alkhouri N. Characterization of patients with both alcoholic and nonalcoholic fatty liver disease in a large United States cohort. *World J Hepatol* 2019; 11(10): 710-718
URL: https://www.wjgnet.com/1948-5182/full/v11/i10/710.htm
DOI: https://dx.doi.org/10.4254/wjh.v11.i10.710

INTRODUCTION

Fat accumulation in the liver, known as fatty liver disease, is a major cause of chronic liver disease worldwide[1]. There are two main classifications of fatty liver disease: alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD). The well-accepted threshold values of alcohol consumption thought to contribute to ALD are 30 g/d for men and 20 g/d for women[2,3]. NAFLD, on the other hand, is considered as the hepatic manifestation of the metabolic syndrome (MetS)[4] and is characterized by the presence of liver steatosis in the absence of other causes of fatty liver disease, particularly significant alcohol consumption. Recently, in the general population, the prevalence of obesity and MetS has been rising[5]; this increase presumably positively correlates with cases of NAFLD. Globally, NAFLD is estimated to afflict approximately 25.24% (95%CI: 22.10-28.65) of the population[6], and is on track to becoming the leading cause of liver transplantation in the near future. Similarly, the prevalence of ALD is on the rise. Currently, it affects nearly 8% of the general population in the United States. Alcohol appears to differentially induce toxic effects on the liver based on sex: It takes approximately twice the volume of alcohol and a longer duration of alcohol consumption for men to develop ALD compared to women[7]. In men, ethnicity appears to affect rates and outcomes of alcoholic cirrhosis:

Incidence is highest in African-Americans followed by Hispanics then Caucasians; however, Hispanic males have the highest mortality rates from alcoholic cirrhosis[8,9].

In a substantial proportion of the population, the risk factors that contribute to each of the two main types of fatty liver disease coexist within a given individual. Alcohol consumption sensitizes the liver to damage induced by MetS and vice versa; this could result in concurrent ALD and NAFLD in the same liver. We propose to call this scenario both alcoholic and NAFLD (BAFLD). We also believe that due to the presence of risk factors for both ALD and NAFLD, patients with BAFLD are at higher risk of advanced fibrosis (AF) and complications related to end-stage liver disease. Studies describing the combined effect of alcohol consumption and MetS on hepatic steatosis are scarce. MetS and excess alcohol consumption are likely responsive to modifiable dietary and lifestyle factors; therefore, understanding their reciprocal interaction and combined effect on the liver might lead to a better understanding of BAFLD pathogenesis as well as strategies for treatment and prevention[10]. The aim of this study was to determine and compare the prevalence and clinical characteristics of BAFLD to NAFLD in a large cohort of subjects in the United States.

MATERIALS AND METHODS

Subjects

All adult (18+ years) subjects who participated in the National Health and Nutrition Examination Survey (NHANES) during 2003-2014 cycles were identified and assessed. The NHANES is a survey program conducted by the National Center for Health Statistics (NCHS), which is part of the Centers for Disease Control and Prevention (CDC). The program is designed to assess the health and nutritional status of adults and children in the United States. It began in the early 1960s and became a continuous program in 1999. It examines a sample of 5000 persons a year from different counties across the United States representing the United States population of all ages. The survey includes interview questionnaires, standardized physical examination, and laboratory tests from blood samples collected at examination centers and analyzed at a central laboratory. The survey was approved by the Institutional Review Board at the Center for Disease Control and Prevention, and informed consent was obtained from all participants.

Diagnosis of NAFLD was made based on elevated alanine aminotransferase (ALT) (> 30 U/L in males and > 19 in females) and being overweight or obese [body mass index (BMI) ≥ 25 kg/m^2) in the absence of other causes of chronic liver disease (viral hepatitis, autoimmune liver disease, metabolic liver disease, total parenteral nutrition and medications *etc*.) Patients with BAFLD met the criteria for NAFLD but also had either MetS or type 2 diabetes and consumed excessive amounts of alcohol defined as ≥ 3 drinks/d for men and ≥ 2 drinks/d for women. The following patients were excluded; reported use of hepatotoxic medications, hepatitis viral infection, missing ALT, missing BMI, no alcohol intake information, missing diabetes status, and missing information on MetS components. MetS was defined as central Obesity plus at least 2 of the following: diabetes, hypertension, hypertriglyceridemia or low high-density lipoprotein cholesterol (HDL).

Demographic variables including age, gender, ethnicity, waist circumference, average drinks a day, smoking status, BMI, central obesity, hypertension, diabetes, triglyceride (TG), HDL, MetS, and other variables were also collected. Laboratory parameters including aspartate aminotransferase (AST), ALT, alkaline phosphatase, platelets, albumin, bilirubin, lipid profile including TG and hemoglobin A1c (HbA1C) were also measured.

To assess for the presence of AF in NAFLD and BAFLD, a non-invasive liver fibrosis score, Fibrosis-4 (FIB-4) index, was calculated using age, AST, ALT and platelet count.

Outcomes

The primary outcome was to assess the prevalence and clinical characteristics of NAFLD and BAFLD. The secondary outcome was to evaluate the prevalence of AF in patients with NAFLD and BAFLD.

Statistical analysis

Data is presented as the mean ± SE or un-weighted frequency (%). The prevalence of NAFLD and BAFLD was assessed by calculating the percent of participants meeting the definitions of each; the corresponding 95%CIs are reported. A subgroup analysis was performed in subjects with either of the two liver diseases. The unadjusted analysis was implemented to evaluate differences between NAFLD and BAFLD;

continuous variables were compared using *t*-tests, and categorical variables were compared using Rao-Scott chi-square tests. A multivariable regression analysis was performed to compare disease severity between the BAFLD and NAFLD groups, after adjusting for diabetes and other components of the metabolic syndrome. Linear regression was used to model FIB-4 score while logistic regression was used to model the presence of suspected AF based on these scores.

All analyses were performed using SAS survey procedures (version 9.4, The SAS Institute, Cary, NC, United States), which account for the complex sampling design of NHANES and appropriately weight participants in statistical models. The full sample MEC exam weights were used in all analyses; weights for combined cycles were constructed following the guidelines provided in the NHANES analytic guidelines.

RESULTS

Prevalence of BAFLD in United States adult population

A total of 20939 subjects met the inclusion criteria during the 2003-2014 cycles. Overall, the prevalence of NAFLD was 25.9% (95%CI: 25.1-26.8), and that of BAFLD was 0.84% (95%CI: 0.67-1.02), which corresponds to an estimated 1.24 million Americans affected by BAFLD as shown in Table 1.

Patient characteristics: The descriptive characteristics of the study participants are shown in Table 2. Compared to patients with NAFLD, patients with BAFLD were more likely to be males, but there were no significant differences in the mean age between the two groups (43.8 *vs* 44.5 years; $P = 0.34$). The BAFLD population had approximately 2.5 times more current smokers than NAFLD group and they also had approximately 16 times a greater number of drinks/d. Given the fact that we used MetS and diabetes mellitus type 2 (DM2) as part of the definition of BAFLD, components of the MetS were more common in the BAFLD cohort. For example, central obesity was also more prevalent in BAFLD patients. In addition, we found significantly higher percentage of MetS in BAFLD group compared to NAFLD population, with high prevalence of HTN, DM, hypertriglyceridemia and low HDL, $P < 0.001$ for all. Patients with BAFLD were more likely to have significantly higher ALT, AST, gamma glutamyl transferase (GGT). Patients with BAFLD also had significantly higher cholesterol and HbA1C than NAFLD patients. Interestingly, compared to NAFLD patients, those with BAFLD had lower platelet counts.

Prevalence of AF in patients with NAFLD and BAFLD

Based on FIB-4 index of 2.67 or higher, patients with BAFLD were found to have significantly higher prevalence of AF compared to the NAFLD group, (7.1% ± 2.5 in the BAFLD group *vs* 1.7% ± 0.22 in the NAFLD group, $P = 0.045$) as seen in Figure 1. Even after adjusting for all the components of MetS, subjects with BAFLD had 3.2 times higher odds of having AF than those with NAFLD [OR (95%CI) for FIB-4 > 2.67 = 3.2 (1.4, 7.0, $P = 0.004$)].

DISCUSSION

To the best of our knowledge, the current study provides novel data on the prevalence and clinical characteristics of BAFLD in the United States adult population. The main findings of our study are the following: (1) BAFLD is common in the United States with an estimated 1.24 million Americans being affected; (2) Compared to NAFLD, patients with BAFLD were more likely to be male and active smokers; (3) They also have higher ALT (53.1 *vs* 38.2 U/L), AST (43.3 *vs* 31.2 U/L), and lower platelet counts (243 *vs* 261 K/uL) ($P < 0.05$ for all); and (4) The prevalence of AF was also significantly higher in patients with BAFLD than subjects with NAFLD with an adjusted OR of having AF being 3.2 (1.4, 7.0) based on the FIB-4 index.

Several studies have highlighted the strong bidirectional association between MetS components and NAFLD[4,11,12]. Obesity is a principle risk factor for both NAFLD and MetS. NAFLD was reported to occur in > 95% of patients with severe obesity undergoing bariatric surgery[13,14]. Between 1980 and 2014, the World Health Organization (WHO) reported a doubling of obesity, with 39% of adults being considered overweight in 2014. In light of this, it is unsurprising that the prevalence of NAFLD is estimated to be close to 25% of the adult population[4,15], which is consistent with our results.

Nearly 70% of the adult population worldwide is estimated to consume alcohol; the highest consumption levels are found in the developed world, particularly Europe and North America[16]. This suggests that the prevalence of ALD in the United States

Table 1 Prevalence of non-alcoholic fatty liver disease, alcoholic liver disease and both alcoholic and non-alcoholic fatty liver disease

Liver disease	Unweighted frequency	Weighted frequency	Prevalence (95%CI)
NAFLD	5351	38151562	25.9 (25.1, 26.8)
BAFLD	170	1243289	0.84 (0.67, 1.02)
ALD	81	590979	0.40 (0.28, 0.52)

Unweighted population total: 20939; Weighted population total: 147169551. NAFLD: Non-alcoholic fatty liver disease; BAFLD: Both alcoholic and non-alcoholic fatty liver disease; ALD: Alcoholic liver disease.

would likely be high as well. Diseases of excess alcohol largely affect men, which could be explained by the fact that men drink more frequently, in larger quantities, and have fewer abstainers than women[16]. However, females are more prone to alcohol-related liver injury upon consuming lesser quantities of alcohol for shorter durations. Determining the relative clinical contributions of alcohol consumption and MetS to fatty liver disease is difficult, especially when both risk factors are present in the same patient. Indeed, it is well known that patients with NAFLD can consume higher amounts of alcohol than previously thought[17]. Obesity/MetS and excessive alcohol consumption may coexist in a significant proportion, affecting the liver in ways that may lead to the development of BAFLD.

Although, there are data addressing the effect of alcohol or obesity on liver[18-21], the interaction between alcohol consumption and obesity/MetS and their effect on liver biochemical variables are not well characterized. Age, sex, and ethnicity affect NAFLD prevalence; the likelihood of men having NAFLD is two times higher than women[6]. In the present study, patients with BAFLD were more likely to be males (75.8% ± 3.9% *vs* 46.9% ± 0.87%) and smokers (45.3% *vs* 17.6%) than patients with NAFLD alone. This is likely due to the larger number of males with alcoholic liver disease and high percentage of male smokers.

Furthermore, our data demonstrate that patients with BAFLD, when compared to the NAFLD group, had higher liver enzymes and lower platelets counts, suggesting more advanced liver disease in these patients. Our results are in concordance with previous studies that implied that the effect of alcohol consumption on hepatic steatosis, as measured by the examination of serum liver enzymes, increased with increasing BMI[22-25]. Hepatic steatosis was only found in 16% of lean controls in the Dionysos study in Northern Italy; however, this prevalence was increased to 46% in subjects with an alcohol intake > 60 g/d and to 76% in the obese participants[26].

Notably, in our study, BAFLD patients had three-times the risk of AF than the NAFLD group. This likely suggests that the combined effect of ALD and NAFLD have a synergistic unfavorable impact on hepatic fibrosis. The mechanism underlying this interaction is not known. Few small studies have assessed the effect of alcohol consumption on the underlying hepatic histopathology in subjects diagnosed with NAFLD. In a cohort of 112 patients with liver biopsies, Petersen *et al*[27] found that the only positive association between weight and fatty liver wass in patients who were overweight and had moderate alcohol consumption. Ekstedt *et al*[28] found faster fibrosis progression in NAFLD patients who consumed alcohol in moderate amounts. Binge drinking and insulin resistance have been reported to be independent risk factors associated with the progression of fibrosis over a mean of 13.8-year interval. In 1997, Naveau *et al*[29] and Raynard *et al*[30] showed that BMI is positively associated with AF in ALD. Obesity may sensitize an individual to alcohol-induced liver injury at a much lower dose. We estimated 1.24 million Americans might be affected by BAFLD with the concomitant three-fold increase in AF; therefore, this is a significant public health issue with important policy implications.

Our results showed significantly higher blood TG (268 mg/dL *vs* 186 mg/dL) in patients with BAFLD compare to patients with NAFLD. We propose that there may be a combined additive or synergistic effect of alcohol and NAFLD on triglycerides. NAFLD is characterized by increases in TG, very-low-density lipoprotein (LDL), apolipoprotein B to apolipoprotein A1 ratio, and small dense LDL in conjunction with low HDL[31]. Similarly, alcohol consumption is a well-known cause of secondary hypertriglyceridemia and it may exaggerate hypertriglyceridemia in primary lipid disorders[32,33]. Therefore, BAFLD patients may have increased cardio vascular disease (CVD) risk and mortality compared to patients with NAFLD. However, these findings should be interpreted with caution given the fact that MetS and DM2 were included in the definition of BAFLD.

Our study has several limitations. It was a cross-sectional study using a large

Table 2 Demographics and clinical variables

Factor (unit)	NAFLD	BAFLD	*P* value
Gender, % ± SE			< 0.001
Male	46.9 ± 0.87[2]	75.8 ± 3.9[1]	
Current smoker, % ± SE	17.6 ± 0.66[2]	45.3 ± 5.2[1]	< 0.001
BMI, mean ± SE	32.4 ± 0.13	33.1 ± 0.56	< 0.001
Overweight (BMI 25+), % ± SE	100.0 ± 0.00	100.0 ± 0.00	
Obese (BMI 30+), % ± SE	57.6 ± 1.04	64.4 ± 4.7	0.18
Severely obese (BMI 40+), % ± SE	11.1 ± 0.63	12.3 ± 3.2	0.7
Waist circumference (cm), mean ± SE	106.5 ± 0.32[2]	111.9 ± 1.3[1]	< 0.001
Average number of drinks/d, mean ± SE	0.26 ± 0.01[2]	4.3 ± 0.22[1]	< 0.001
Central obesity, % ± SE	79.2 ± 0.86[2]	92.3 ± 2.5[1]	< 0.001
HTN (MS), % ± SE	43.5 ± 1.03[2]	74.7 ± 3.8[1]	< 0.001
Diabetes (MS), % ± SE	20.5 ± 0.68[2]	38.1 ± 5.0[1]	< 0.001
Low HDL, % ± SE	47.2 ± 1.05	49.5 ± 4.7	< 0.001
Hypertriglyceridemia, % ± SE	48.5 ± 1.02[2]	82.3 ± 2.9[1]	< 0.001
Metabolic Syndrome, % ± SE	42.6 ± 1.04[2]	91.4 ± 2.6[1]	< 0.001
Platelet count (1000 cells/uL), mean ± SE	261.4 ± 1.2[2]	243.1 ± 5.7[1]	0.007
ALT (U/L), mean ± SE	38.2 ± 0.32[2]	53.1 ± 3.6[1]	< 0.001
AST (U/L), mean ± SE	31.2 ± 0.34[2]	43.3 ± 3.3[1]	< 0.001
Alkaline phosphatase (U/L), mean ± SE	71.4 ± 0.51	76.7 ± 3.4	0.01
Total bilirubin (mg/dL), mean ± SE	0.72 ± 0.01	0.77 ± 0.02	0.007
Creatinine (mg/dL), mean ± SE	0.86 ± 0.00	0.86 ± 0.01	0.15
Cholesterol (mg/dL), mean ± SE	206.8 ± 0.79[2]	224.7 ± 4.3[1]	< 0.001
Triglycerides (mg/dL), mean ± SE	186.6 ± 2.8[2]	268.0 ± 17.2[1]	< 0.001
HDL (mg/dL), mean ± SE	48.3 ± 0.30	48.3 ± 1.7	< 0.001
LDL (mg/dL), mean ± SE	121.2 ± 0.71	122.8 ± 4.8	< 0.001
Gamma glutamyl transferase (U/L), mean ± SE	36.6 ± 0.62[2]	94.6 ± 16.4[1]	0.002
Glycohemoglobin (%), mean ± SE	5.6 ± 0.02	5.7 ± 0.09	< 0.001
FIB-4, mean ± SE	0.94 ± 0.01[2]	1.2 ± 0.09[1]	0.001
FIB-4 > 2.67, % ± SE	1.7 ± 0.22	7.1 ± 2.5	0.045

Population weighted means or percentages are presented with corresponding SE.
[1]Significantly different from NAFLD;
[2]Significantly different from BAFLD. Post-hoc comparisons were done using Bonferroni correction. NAFLD: Non-alcoholic fatty liver disease; BAFLD: Both alcoholic and non-alcoholic fatty liver disease; BMI: body mass index; HTN: Hypertension; HDL: High density lipoprotein; LDL: Low density lipoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; FIB-4: Fibrosis-4.

national database; thus, chronological relationships could not be established. The use of elevated ALT and BMI to define patients with NAFLD is imperfect and may have included patients who do not actually have NAFLD and excluded lean subjects that have non-obese NAFLD. However, given the large population-based study sample, we considered this definition to be the most suitable for this study. We used the non-invasive fibrosis score to predict AF which has been previously used in NHANES studies, as it was impossible to perform liver biopsies or even fibro-scans in such a large cohort[34]; however, it is not the gold-standard. We did not use the AST/ ALT ratio or aspartate aminotransferase to platelet ratio index (APRI) to diagnose AF given their heavy reliance on AST values, which are known to be affected by alcohol consumption. Similarly, we did not use the NAFLD fibrosis score because diabetes is one of its components and this may have biased our estimates of AF. Using a large, national, population-based sample allows for the ability to generalize our results to the United States population and offsets these limitations.

In conclusion, a substantial percentage of the general American population may have BAFLD. Patients with BAFLD tend to have more advanced disease and may have a higher risk of progression to cirrhosis or end-stage liver disease. Therefore, future research should aim to identify the burden of liver disease in this population and intervene in a timely fashion. The risk of the combined effects of MetS and alcohol consumption should be taken seriously in all patients with suspected NAFLD.

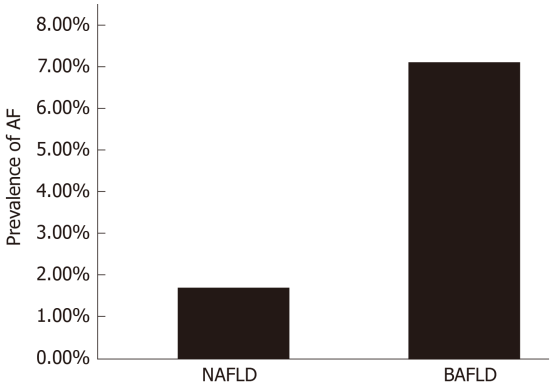

Figure 1 The prevalence of advanced fibrosis in patients with non-alcoholic fatty liver disease (1.7%) and both alcoholic and non-alcoholic fatty liver disease (7.1%). Patients with BAFLD have 3-fold increase in the prevalence of advanced fibrosis. NAFLD: Non-alcoholic fatty liver disease; BAFLD: Both alcoholic and non-alcoholic fatty liver disease; AF: Advanced fibrosis.

Importantly, screening for risky, often under-reported, alcohol consumption should be considered. Data on safe alcohol consumption in NAFLD is conflicting and needs further assessment in future prospective studies.

ARTICLE HIGHLIGHTS

Research background

Fatty liver disease caused by excess alcohol consumption is called alcoholic liver disease (ALD) whereas fatty liver disease caused by metabolic disease is called non-alcoholic fatty liver disease (NAFLD). Often, risk factors for both types of fatty liver diseases occur in the same individual, especially as the prevalence of both of these diseases is on the rise. The presence of both types of fatty liver disease in one individual may lead to the development of a new condition we call both alcoholic and NAFLD (BAFLD). We believe that patients with BAFLD are at a higher risk of advanced fibrosis and complications related to end-stage liver disease. Studying and understanding BAFLD has important public health and policy implications.

Research motivation

A new fatty liver entity, we call BAFLD, occurs when both ALD and NAFLD risk factors are present in the same individual. We reported on the clinical characteristics and degree of liver fibrosis in BAFLD patients compared to NAFLD patients. As most of the risk factors that lead to BAFLD are modifiable dietary and lifestyle choices, understanding their reciprocal interaction and combined effect on the liver might lead to a better understanding of BAFLD pathogenesis, treatment, and prevention. This has important public health and policy implications.

Research objectives

This study aimed to identify the prevalence of NAFLD and BAFLD and to assess the clinical characteristics of patients with BAFLD in comparison to those with NAFLD in a large cohort of subjects in the United States.

Research methods

This is a cross-sectional study that was done using National Health and Nutrition Examination Survey between 2003-2014. NAFLD and BAFLD patients were identified. Univariable and multivariable analysis were performed to assess differences between NAFLD and BAFLD and to compare severity based on a validated fibrosis score (FIB4 index).

Research results

The prevalence of NAFLD was at 25.9% and that of BAFLD was 0.84% which corresponds to an estimated 1.24 million Americans affected by BAFLD. Compared to NAFLD, patients with BAFLD were more likely to be male, smokers, have higher ALT, AST, triglycerides, and lower platelets; $P < 0.01$ for all. More importantly, after adjusting for MetS components, BAFLD patients were significantly about three times more likely to have advanced fibrosis based on FIB4 index > 2.67, $P = 0.004$].

Research conclusions

In conclusion, a substantial percentage of the general American population may have BAFLD. Patients with BAFLD tend to have more advanced disease and may have a higher risk of progression to cirrhosis and end-stage liver disease. Therefore, special attention should be paid to this population to identify the burden of liver disease and intervene in a timely fashion.

Research perspectives

The possibility of the combined effects of MetS and alcohol consumption should be considered in all patients with suspected NAFLD. Vitally, consideration should be given to the role of screening for identification of risky, often under-reported, alcohol consumption. Data on safe alcohol consumption in NAFLD is conflicting and needs further assessment in future prospective studies.

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World Journal of Hepatology

Submit a Manuscript: https://www.f6publishing.com

World J Hepatol 2019 October 27; 11(10): 719-724

DOI: 10.4254/wjh.v11.i10.719

ISSN 1948-5182 (online)

CASE REPORT

Escitalopram-induced liver injury: A case report and review of literature

Qin Xiang Ng, Christl Suet Kwan Yong, Wayren Loke, Wee Song Yeo, Alex Yu Sen Soh

ORCID number: Qin Xiang Ng (0000-0001-8561-2513); Christl Suet Kwan Yong (0000-0003-3437-9891); Wayren Loke (0000-0003-4498-9773); Wee Song Yeo (0000-0002-2201-2673); Alex Yu Sen Soh (0000-0002-1981-1941).

Author contributions: Ng QX conceived, designed and carried out the study, and the relevant data analysis and interpretation, while Soh AYS supervised the study; Yong CSK, Loke WR, Soh AYS and Yeo WS carried out the study, and the relevant data analysis and interpretation; All authors contributed to the writing and proofreading of the final manuscript; The final manuscript was discussed and approved by all authors.

Informed consent statement: Written consent was obtained from the patient.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Qin Xiang Ng, Christl Suet Kwan Yong, Institute of Mental Health, Buangkok Green Medical Park, Singapore 539747, Singapore

Qin Xiang Ng, Christl Suet Kwan Yong, Wayren Loke, MOH Holdings Pte Ltd, Singapore 099253, Singapore

Wee Song Yeo, Alex Yu Sen Soh, National University Hospital, National University Health System, Singapore 119074, Singapore

Wee Song Yeo, Alex Yu Sen Soh, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 117597, Singapore

Corresponding author: Qin Xiang Ng, MBBS, Institute of Mental Health, Buangkok Green Medical Park, 10 Buangkok View, Singapore 539747, Singapore. ng.qin.xiang@u.nus.edu
Telephone: +65-66386979

Abstract

BACKGROUND

Depression is a growing public health problem that affects over 350 million people globally and accounts for approximately 7.5% of healthy years lost due to disability. Escitalopram, one of the first-line medications for the treatment of depression, is a selective serotonin reuptake inhibitor and one of the most commonly prescribed antidepressant medications worldwide. Although thought to be generally safe and with minimal drug-drug interactions, we herein present an unusual case of cholestatic liver injury, likely secondary to escitalopram initiation.

CASE SUMMARY

A 56-year-old Chinese lady presented with fever and cholestatic liver injury two weeks after initiation of escitalopram for the treatment of psychotic depression. Physical examination was unremarkable. Further investigations, including a computed tomography scan of the abdomen and pelvis and tests for hepatitis A, B and C and for autoimmune liver disease were unyielding. Hence, a diagnosis of escitalopram-induced liver injury was made. Upon stopping escitalopram, repeat liver function tests showed downtrending liver enzymes with eventual normalization of serum aspartate aminotransferase and alanine aminotransferase one-week post-discharge.

CONCLUSION

Clinicians should be aware of the possibility of escitalopram-induced liver injury when initiating depressed patients on antidepressant treatment. This requires

Manuscript source: Unsolicited manuscript

Received: July 21, 2019
Peer-review started: July 24, 2019
First decision: August 7, 2019
Revised: August 20, 2019
Accepted: October 2, 2019
Article in press: October 2, 2019
Published online: October 27, 2019

P-Reviewer: Khoury T, Yeoh SW, Zapater P
S-Editor: Ma YJ
L-Editor: A
E-Editor: Ma YJ

extra vigilance as most patients may remain asymptomatic. Measurement of liver function tests could be considered after initiation of antidepressant treatment, especially in patients with pre-existing liver disease.

Key words: Depression; Antidepressant; Escitalopram; Liver injury; Drug-induced; Drug-induced liver injury

Core tip: We herein report a probable case of escitalopram-induced liver injury. A 56-year-old Chinese lady presented with fever and cholestatic liver injury two weeks after initiation of escitalopram for the treatment of psychotic depression. Physical examination and investigations for stones, viral hepatitis and autoimmune liver disease were unyielding. Upon stopping escitalopram, repeat liver function tests showed downtrending liver enzymes with eventual normalization of serum aminotransferase levels. Clinicians should be aware of the possibility of drug-induced liver injury associated with escitalopram use, when initiating depressed patients on antidepressant treatment. This requires extra vigilance as most patients may remain asymptomatic.

Citation: Ng QX, Yong CSK, Loke W, Yeo WS, Soh AYS. Escitalopram-induced liver injury: A case report and review of literature. *World J Hepatol* 2019; 11(10): 719-724
URL: https://www.wjgnet.com/1948-5182/full/v11/i10/719.htm
DOI: https://dx.doi.org/10.4254/wjh.v11.i10.719

INTRODUCTION

Depression is a growing public health problem that affects over 350 million people globally and accounts for approximately 7.5% of healthy years lost due to disability[1]. Escitalopram is a selective serotonin reuptake inhibitor (SSRI) and one of the most commonly prescribed antidepressant medications worldwide[2]. Although thought to be generally safe and with minimal drug-drug interactions[3], we herein present an unusual case of cholestatic liver injury, likely secondary to escitalopram initiation.

CASE PRESENTATION

This patient was a 56-year-old Chinese lady transferred to our hospital for fever and deranged liver enzymes for investigation. She was receiving treatment at a psychiatric hospital for psychotic depression prior. At presentation, she was asymptomatic and did not have any localizing signs of infection. She had no cough, sore throat, rhinorrhea, diarrhea or dysuria. There was no change in the colour of her urine or stools. She had no constitutional symptoms or significant weight loss over the past 6 mo, and no chills, rigors or night sweats throughout. She did not consume any raw foods or herbal supplements and had not travelled outside of Singapore in the recent years. Her past medical history was significant for psychotic depression, for which she was being managed with escitalopram 5 mg once daily and olanzapine 7.5 mg twice daily. She had started escitalopram and olanzapine two weeks prior to presentation. She had no known drug allergies.

On physical examination, she had an average build (body mass index 22.8 kg/m^2), was not jaundiced, had no rash present, and did not have any tattoos or needle track marks. On palpation, her abdomen was soft and non-tender, and there were no palpable masses or organomegaly. Physical examination was unremarkable. There was no palpable cervical, axillary, supraclavicular, or inguinal lymph nodes.

Laboratory studies revealed a normochromic, normocytic anemia (as confirmed on a peripheral blood film) with a haemoglobin level of 10.1 g/dL. Lactate dehydrogenase (LDH) and haptoglobin were within normal limits. Total whites were not raised at 5.4 × 10^9 cells/L and eosinophils count were within normal limits as well (0.33 × 10^9 cells/L). The C-reactive protein was elevated at 67.5 mg/L, erythrocyte sedimentation rate was 10 mm/h and two sets of peripheral aerobic and anaerobic blood cultures showed no bacterial growth after 72 h. Her thyroid function test (TSH and free T_4), serum electrolytes, urea and creatinine were all within normal limits,

while her liver panel showed raised alanine aminotransferase (ALT, 183 U/L), aspartate aminotransferase (AST, 99 U/L), alkaline phosphatase (ALP, 552 U/L) and GGT (510 U/L).

A hepatitis screen was done, which found that antibodies against hepatitis C virus were non-reactive, the surface antigen of the hepatitis B virus was non-reactive as well and anti-HBs was >1000 IU/L. This indicated recovery from (and immunity to) the hepatitis B virus (HBV) or successful immunization with HBV vaccine. She had received Hepatitis A and B vaccinations as a young adult.

Serum autoantibodies were performed and included antinuclear antibody of <1:640, speckled pattern, negative anti-smooth muscle antibody titre, and negative antimitochondrial M2 antibody.

In terms of imaging, a computed tomography of the abdomen and pelvis found no pancreatic or other mass. Hepatic parenchymal attenuation was normal, with no focal lesions noted. There were no radio-opaque gallstones or biliary dilatation.

FINAL DIAGNOSIS

Given the history, examination and investigation findings, a diagnosis of drug-induced liver injury (DILI) was made.

Although olanzapine has also been linked to reports of DILI[4], it was precluded as a culprit drug in this case because the patient had previously taken it with no issues. She was treated with oral olanzapine 10 mg nightly and oral fluoxetine 20 mg every morning in February 2018 for psychotic depression, with good resolution of symptoms and the drugs were subsequently tapered and stopped by December 2018.

The Roussel Uclaf Causality Assessment Method (RUCAM) scoring[5] also helps clinicians determine how likely the diagnosis of DILI is. The components considered are: (1) time to onset (+1 or +2); (2) course (-2, 0, +1, +2 or +3); (3) risk factors (2 scores: 0 or +1 each); (4) concomitant drugs (0, -1, -2 or -3); (5) nondrug causes of liver injury (-3, -2, 0, +1, or +2); (6) previous information on the hepatotoxicity of the drug (0, +1, or +2); and (7) response to rechallenge (-2, 0, +1, or +3)[5]. Applying the RUCAM scoring to our patient, escitalopram yielded a total score of at least 5, suggesting that it was a 'probable' cause of DILI.

TREATMENT

Escitalopram, which was newly initiated, was suspected to be the culprit drug based on the temporal sequence (Figure 1), the fact that it undergoes extensive hepatic metabolism[6] and its overall likelihood of DILI based on RUCAM scoring. Treatment was thus withdrawal of escitalopram.

OUTCOME AND FOLLOW-UP

Our patient had no further temperature spikes while inpatient. Upon stopping escitalopram, repeat liver function tests showed downtrending liver enzymes with eventual normalization of serum AST and ALT one week post-discharge (Table 1). Patient remained well and asymptomatic.

DISCUSSION

Drug-induced liver injury (DILI) is one of the leading causes of hepatic failure in the Western world[7]. It is often a difficult diagnosis to make as it relies largely on the exclusion of other potential causes[8]. A detailed drug chart in relation to the timing of onset of liver injury and recovery after the implicated agent is stopped can help clinch the diagnosis. In this patient, as she presented with fever and deranged liver enzymes, it was vital to consider gallstone disease, viral hepatitis, or autoimmune liver disease. CT scan of the abdomen and pelvis and tests for hepatitis A, B and C and for autoimmune liver disease were negative.

While a liver biopsy is not always indicated, in DILI, liver biopsy shows only non-specific findings, none of the features are pathognomonic. However, liver biopsy may help in cases where there is ambiguity and other causes (*e.g.*, autoimmune liver disease or hepatitis flare) are possible differentials. RUCAM scoring also helps clinicians determine how likely the diagnosis of DILI is.

Depending on the pattern of hepatic injury, DILI can be classified as hepatocellular,

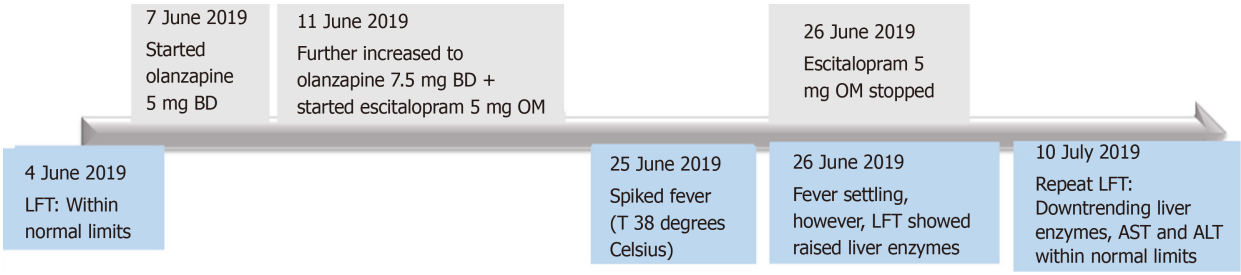

Figure 1 A detailed drug chart in relation to the timing of onset of liver injury. BD: Twice daily; OM: Every morning; LFT: Liver function test; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; T: Temperature.

cholestatic, or mixed[9]. Hepatocellular injury is marked by elevated serum ALT with a small or no increase in ALP levels; an associated high serum bilirubin level, found in cases of severe hepatocellular damage, connotes poor prognosis[9]. While cholestatic liver injury, as in the case of our patient, is characterized by markedly elevated serum ALP and only slightly higher than normal ALT levels. In cases of mixed injury, both ALT and ALP levels are elevated.

With regard to the pathophysiology of DILI, it is thought to be due to direct, indirect or idiosyncratic hepatotoxicity[8]. In the case of escitalopram, it is extensively metabolized by the liver, mainly via the cytochrome P450 system (CYP3A4, CYP2C19 and, to a lesser extent, CYP2D6)[3] and hepatotoxicity may be due to toxic intermediates (Figure 2). In literature, there is only one published case report of a 30 year-old woman who developed cholestatic liver injury[10], marked by jaundice and pruritus 2 mo after starting citalopram (citalopram is a racemic mixture, while escitalopram is the therapeutically active S-enantiomer). Citalopram was dosed at 10 mg daily for 1 month, followed by 20 mg daily. Similar to our patient, she had previously tried fluoxetine (another SSRI antidepressant) with no issues.

In the case of our patient, we are unable to entirely exclude the fact that olanzapine may have also contributed to her liver injury as olanzapine also undergoes extensive hepatic metabolism by CYP1A2 and to a lesser extent by CYP2D6[11]. Olanzapine has also been reported to cause transient serum liver enzyme elevations[4].

According to the results of a multicenter drug surveillance program of 184234 psychiatric inpatients treated with antidepressants between 1993 and 2011 in 80 psychiatric hospitals, 149 cases of DILI (0.08%) were reported[12]. However, the risk of antidepressant-induced liver injury is likely underestimated as most patients are asymptomatic, especially during early stages of DILI.

DILI is thought to be dose-independent, albeit there could be some dose-dependent aspects as DILI tended to occur at high median dosages[12]. In terms of choice of psychotropic medication, theoretically speaking, drugs that are not metabolized extensively and primarily renally excreted are probably the safest in patients with pre-existing liver disease. These drugs include paliperidone[13], sulpiride[14] and amisulpride[15].

CONCLUSION

Although thought to be generally safe and with minimal drug-drug interactions, clinicians should be aware of the possibility of escitalopram-induced liver injury when initiating depressed patients on antidepressant treatment. This requires extra vigilance as most patients may remain asymptomatic. It is still controversial whether routine monitoring is recommended, especially in patients with pre-existing liver disease. Fortunately, DILI is typically reversible after withdrawal of the implicated drug and patients should have a favourable outcome.

Table 1 Liver function test trend (with abnormal values highlighted in bold)

Test	4 June 2019	26 June 2019	27 June 2019	10 July 2019	24 July 2019
Albumin (g/L)	35	35	34	39	36
AST (U/L)	28	99	67	27	22
ALT (U/L)	32	183	150	30	22
GGT (U/L)	25	510	495	275	144
ALP (U/L)	102	552	585	237	123
Bilirubin, total (μmol/L)	17	24	11	12	7
Protein, total (g/L)	69	72	74	78	69
Globulin (g/L)	35	38	40	39	33

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase.

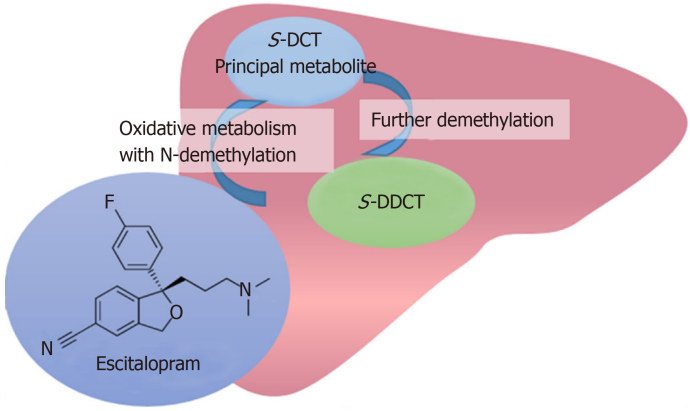

Figure 2 Hepatic metabolism of escitalopram; *S*-demethylcitalopram, the principal metabolite, is present at one-third the level of escitalopram and the didemethyl metabolite of escitalopram is typically present at or below quantifiable concentrations.

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