Digestive Diseases

Liver: Research Article

Dig Dis 2023;41:780–788
DOI: 10.1159/000529914

Received: March 17, 2022
Accepted: February 8, 2023
Published online: June 26, 2023

Efficacy of Co-Medications in Patients with Alcoholic Liver Disease

Timo Itzel[a, b] Thomas Falconer[c] Ana Roig[a, b] Jimmy Daza[a, b] Jimyung Park[d] Jae Youn Cheong[e] Rae Woong Park[d, f] Isabella Wiest[a, b] Matthias P. Ebert[b, g] George Hripcsak[c] Andreas Teufel[a, b]

[a]Division of Hepatology, Division of Bioinformatics, Department of Medicine II, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; [b]Clinical Cooperation Unit Healthy Metabolism, Center for Preventive Medicine and Digital Health Baden-Württemberg (CPDBW), Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; [c]Department of Biomedical Informatics, Columbia University Irving Medical Center, New York, NY, USA; [d]Department of Biomedical Sciences, Ajou University Graduate School of Medicine, Suwon, South Korea; [e]Department of Gastroenterology, Ajou University School of Medicine, Suwon, South Korea; [f]Department of Biomedical Informatics, Ajou University School of Medicine, Suwon, South Korea; [g]Department of Medicine II, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

Downloaded from http://karger.com/ddi/article-pdf/41/5/780/3995630/000529914.pdf by Universitätsbibliothek Heidelberg user on 23 October 2024

Keywords
Alcoholic liver disease · Survival · Cohort · Medication

Abstract
Background: Alcoholic liver disease (ALD) is still increasing and leads to acute liver injury but also liver cirrhosis and subsequent complications such as liver failure or hepatocellular carcinoma (HCC). As most patients fail to achieve alcohol abstinence, it is essential to identify alternative treatment options in order to improve the outcome of ALD patients. ***Methods:*** Evaluating two large cohorts of patients with ALD from the USA and Korea with a total of 12,006 patients, we investigated the effect on survival of aspirin, metformin, metoprolol, dopamine, and dobutamine drugs in patients with ALD between 2000 and 2020. Patient data were obtained through the "The Observational Health Data Sciences and Informatics consortium," an open-source, multi-stakeholder, and interdisciplinary collaborative effort. ***Results:*** The use of aspirin ($p = 0.000$, $p = 0.000$), metoprolol ($p = 0.002$, $p = 0.000$), and metformin ($p = 0.000$, $p = 0.000$) confers a survival benefit for both AUSOM- and NY-treated cohorts. Need of catecholamines dobutamine ($p = 0.000$, $p = 0.000$) and dopamine ($p = 0.000$, $p = 0.000$) was strongly indicative of poor survival. β-Blocker treatment with metoprolol ($p = 0.128$, $p = 0.196$) or carvedilol ($p = 0.520$, $p = 0.679$) was not shown to be protective in any of the female subgroups. ***Conclusion:*** Overall, our data fill a large gap in long-term, real-world data on patients with ALD, confirming an impact of metformin, acetylsalicylic acid, and β-blockers on ALD patient's survival. However, gender and ethnic background lead to diverse efficacy in those patients.

© 2023 S. Karger AG, Basel

Introduction

Alcohol consumption is a global healthcare problem resulting in serious pathological changes causing acute liver injury such as alcoholic hepatitis but also liver cirrhosis and subsequent complications such as liver

karger@karger.com
www.karger.com/ddi

© 2023 S. Karger AG, Basel

Correspondence to:
Andreas Teufel, andreas.teufel@medma.uni-heidelberg.de

Karger

failure or hepatocellular carcinoma (HCC). Taken together, these alcohol-related affections are referred to as alcohol-related liver disease (ALD). According to the Global Status Report on Alcohol and Health 2018 by the World Health Organization (WHO), 57% of the population over the age of 15 years (3.1 billion people) has consumed alcohol in the last 12 months, and 2.3 billion people are current drinkers. Overall, the global burden for ALD is rapidly increasing [1]. Thus, ALD remains a threatening and mortal disease [2], frequently requiring medical treatment.

The main treatment for ALD is long-term alcohol abstinence. However, as many patients have difficulties restraining alcohol use but also depending on the degree of complications caused by ALD, other (drug treatment) options are repeatedly considered [2, 3]. Liver transplantation remains the only valid therapeutic option. However, in some countries, e.g., Germany, this option may only be available after 6 months of abstinence, which again is elusive in many patients.

As drugs such as acetylsalicylic acid (ASA), antidiabetic medications such as metformin, or statins were considered to lower HCC risk in patients with chronic liver disease in general, they may also be of interest in ALD [4]. However, very little is known about the benefit of these drugs in ALD without liver cancer. In particular, long-term register data are not available. Also, comparative analyses with respect to gender or ethnic background are widely lacking. Given the impact of ALD on public health and the undisputed urgent need to provide novel preventive and therapeutic strategies, we performed a large register study on two large cohorts – Western and Asian patients – of patients with ALD in order to evaluate the efficacy of diverse medications for these patients.

Patients and Methods

Package for Managing and Analyzing

All patient data were extracted from electronic health records, collected and stored by The Observational Health Data Sciences and Informatics (OHDSI, https://www.ohdsi.org) consortium, a multi-stakeholder, interdisciplinary collaborative to promote value of health data through large-scale analytics. All data were standardized to the OMOP Common Data Model (common terminologies, vocabularies, coding schemes) which allows for the systematic analysis of disparate observational databases. Obtained data were queried using R statistical software (https://www.r-project.org).

R Package AlcoholicLiverDisease

In order to search and analyze the collected data, we created a specific R package "AlcoholicLiverDisease," which is freely available at https://github.com/ohdsi-studies/AlcoholicLiverDisease. Connection between the database and our R package was performed using the R DatabaseConnector package (https://cran.r-project.org/web/packages/DatabaseConnector/). In order to support different SQL database dialects, we used the SqlRender package (https://cran.r-project.org/web/packages/SqlRender), translating our SQL template script into the specific target SQL dialect.

Database Queries OHDSI

All queries were executed fully analyzed on the local databases of Columbia University and Ajou University. Once finished, the results were manually sent to the study coordinating center at the Division of Hepatology, Department of Medicine II, Medical Faculty Mannheim, Heidelberg University. Further analysis at the study coordinating center was therefore fully anonymized.

Patient Inclusion

All patients who had an OHDSI database entry "Alcoholic liver damage (OHDSI ID 201612)" or any of the downstream linked terms such as "Alcoholic fatty liver" (OHDSI ID 193256), "Alcoholic cirrhosis" (OHDSI ID 196463), "Acute alcoholic liver disease" (OHDSI ID 201343), "Alcoholic liver damage" (OHDSI ID 201612), "Zieve's syndrome" (OHDSI ID 4195620), "Chronic alcoholic hepatitis" (OHDSI ID 4146181), "Alcoholic hepatic failure" (OHDSI ID 4340386), "Alcoholic hepatitis" (OHDSI ID 4340383), "Chronic alcoholic liver disease" (OHDSI ID 37017009) and "Acute on chronic alcoholic liver disease" (OHDSI ID 37017151) were selected. Only patients in whom the diagnosis was established after January 1, 2000, were included in our study. Furthermore, all patients with concomitant viral hepatitis (OHDSI ID 4291005) inclusive any of the downstream dependent concepts/terms were also excluded in order to have a very well-defined ALD cohort. For survival analysis, we furthermore enriched the local analysis table with information on the death date. This date was specified to occur after initial documentation of ALD. Time to event was calculated by the time difference in days between the documented date of diagnosis (OHDSI condition_era_start_date out of the condition_era table) and either the death date or last patient contact (OHDSI observation_period_end_date out of the obeservation_period table), if death date was not available.

The need for informed consent was waived by the Columbia University Institutional Review Board, approval number AAAO-7805, last approved on March 22, 2022. At Ajou University, the study was approved by the Institutional Review Board, approval number AJOUIRB-MDB-2021-635.

Evaluation of Treatment Efficacy

All patients were queried for administered drugs, diagnosis, and procedures. Available drug information was extracted from the OHDSI drug_exposure table if the drug_exposure_date was documented after (later) the concondition_era_start_date. Subsequently, these drugs were manually searched for treatment efficacy with respect to patient's survival. For associated survival analysis, the cohort was divided into two groups: treatment and non-treatment for each individual drug, diagnosis, or procedure.

Survival/Kaplan-Meier Analysis

The final survival analysis was performed using the R survival package (https://cran.r-project.org/web/packages/survival).

Downloaded from http://karger.com/ddi/article-pdf/41/5/780/3995630/000529914.pdf by Universitätsbibliothek Heidelberg user on 23 October 2024

Table 1. Patient characteristics

	Columbia University		Ajou University	
	n	%	*n*	%
Patients, *n*	4,667	100.00	7,339	100.00
Male	3,320	71.14	6,661	90.76
Female	1,347	28.86	678	9.24
GI bleeding	877	18.79	688	9.37
Cirrhosis	2,933	62.85	3,287	44.79
Beta-blockers	1,677	35.93	1,641	22.36
Transplant	167	3.58	116	1.58
Fibrosis	32	0.69	15	0.20
Encephalopathy	743	15.92	51	0.69
HCC	117	2.51	419	5.71
Alcoholic-induced organic and mental disorder	1,304	27.94	286	3.90
Schizophrenia	102	2.19	4	0.05
Ascites	1,498	32.10	643	8.76
Hepatitis B	0	0.00	0	0.00
Hepatitis C	0	0.00	0	0.00

Code Availability

All project-specific programming code is freely available from https://github.com/ohdsi-studies/AlcoholicLiverDisease.

Results

Patient Characteristics

Overall, we investigated 12,006 patients with ALD. Of those, 7,339 were treated at Ajou University Gyeonggi Province (AUSOM) in South Korea and 4,667 were treated at Columbia University, New York (Table 1). The Columbia University cohort (NYC) was demonstrated to include a significantly higher number of patients with advanced cirrhosis compared to the AUSOM cohort (63% vs. 48%). Also, complications of cirrhosis such as GI bleeding (18.8% vs. 9.3%) or ascites (32.1% vs. 8.8%) were significantly more prominent in the NYC cohort. In addition, the rate of alcoholic-induced organic and mental disorder was much higher in the NYC cohort as compared to the AUSOM cohort (28% vs. 3.9%). As per database selection, none of those patients suffered from documented chronic hepatitis B or C (Table 1).

Effect of Common Co-Medications on ALD

ASA or Aspirin

For both AUSOM and NYC cohorts, patients taking ASA showed significantly better survival in comparison to the non-treated group. Of note, the AUSOM cohort presents very high survival indexes for both treated and non-treated patients. In contrast, the NY cohort reflects an overall faster decay in survival numbers. However, there is a significant difference between treated and non-treated groups ($p = 0.000$, Fig. 1) and ASA use was associated with a highly significantly improved survival in both cohorts (Fig. 1).

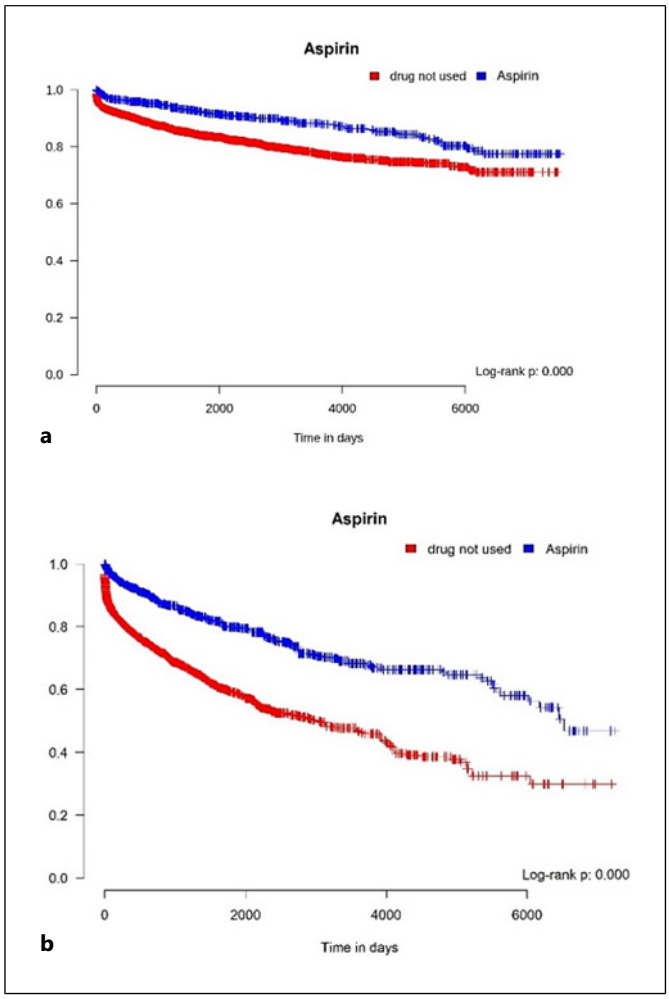
In gender-specific subgroups, effects of ASA on ALD patient's survival remained significant in male patients of both the AUSOM and NYC cohorts (NYC male $p = 0.000$, AUSOM male $p = 0.000$, online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000529914). However, in female patients, a significance of ASA treatment with respect to survival efficacy was not observed (AUSOM female $p = 0.361$, online suppl. Fig. 1).

Metformin

Similarly, metformin seems to confer a slight protection to both AUSOM and NYC patients in comparison to results from non-treated individuals. As depicted in Figure 2, for patients treated with metformin, the NYC cohort was demonstrated to exhibit a definitely larger difference between treated and non-treated groups as compared to the AUSUM cohort. However, the observed differences in survival were highly statistically significant in both cohorts ($p = 0.000$).

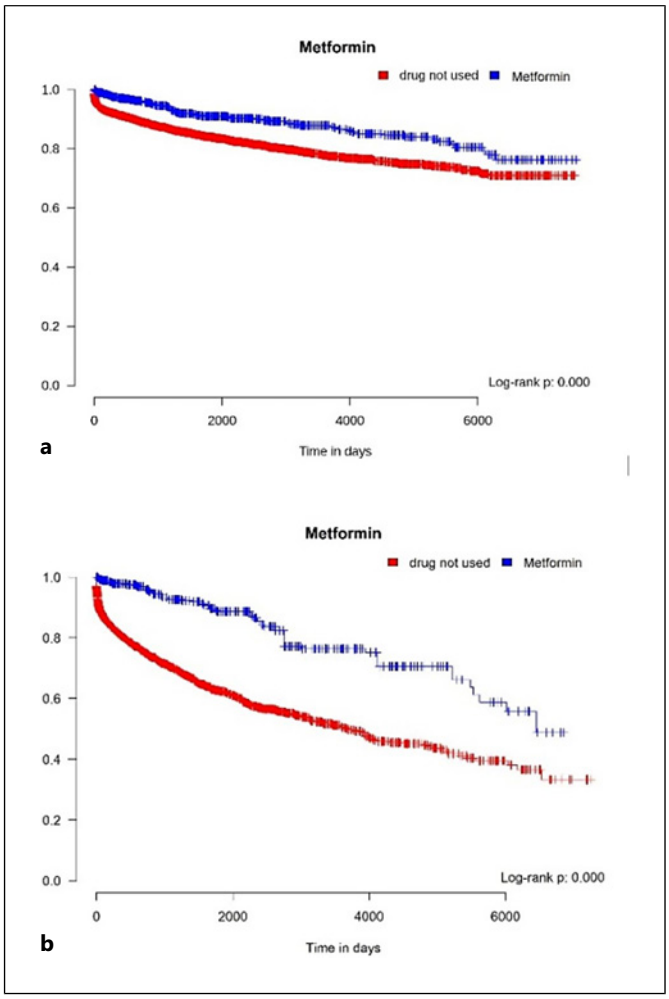
We again investigated gender-specific subgroups. In both cohorts, AUSOM and NYC, effects of ASA on ALD patient's survival remained significant in both genders, male and female (NYC male $p = 0.000$, NYC female $p = 0.000$, AUSOM male $p = 0.000$, AUSOM female $p = 0.023$, online suppl. Fig. 2).

Downloaded from http://karger.com/ddi/article-pdf/41/5/780/3995630/000529914.pdf by Universitätsbibliothek Heidelberg user on 23 October 2024



Color version available online

Fig. 1. ALD patient's survival. **a** AUSOM cohort treated with aspirin (blue line) and non-treated (red line). **b** NYC cohort treated with aspirin (blue line) and non-treated patients (red line).



Color version available online

Fig. 2. ALD patient's survival. **a** AUSOM cohort treated with metformin (blue line) and non-treated (red line). **b** NYC cohort treated with metformin (blue line) and non-treated patients (red line).

β-Blocker: Metoprolol

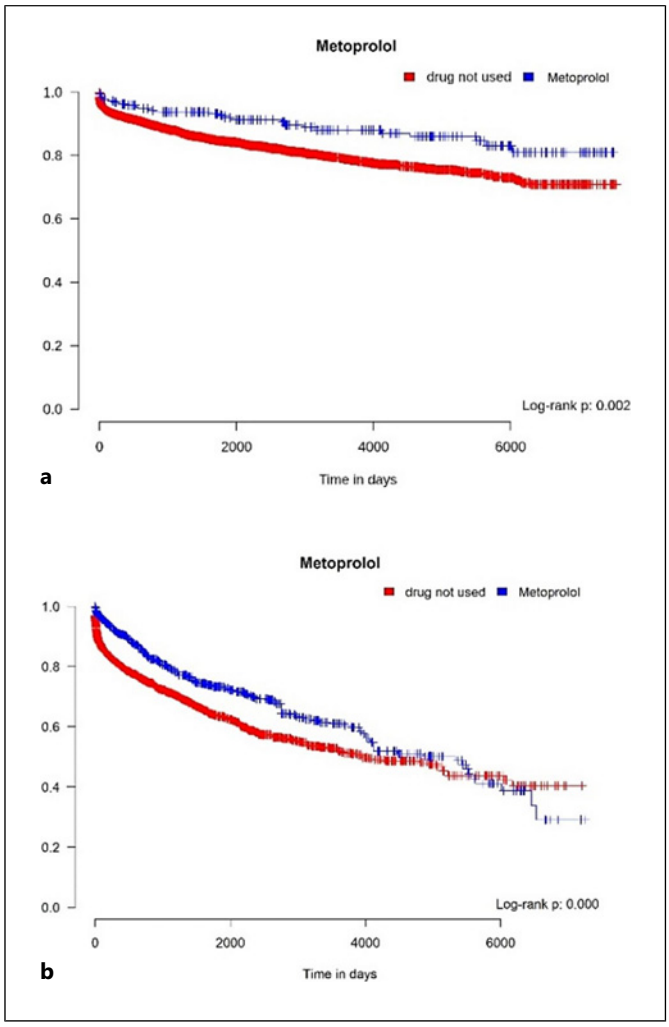
Metoprolol presents a similar pattern or effect on AUSOM and NYC cohorts as ASA and metformin. In general, the survival analysis pointed out metoprolol as a drug conferring a beneficial impact on ALD patients in comparison to the non-treated group. Those differences were statistically significant for both AUSOM and NYC cohorts ($p = 0.002$ and $p = 0.000$, respectively, Fig. 3). Of interest, for both cohorts, gender-specific subgroup analysis revealed significance for metoprolol treatment only in males (males NYC $p = 0.000$, males AUSOM $p = 0.007$, females NYC $p = 0.196$, females AUSOM $p = 0.128$, online suppl. Fig. 3).

β-Blocker: Carvedilol

In contrast to metoprolol, carvedilol did not cause significant differences in survival among Asian patients in the AUSOM cohort ($p = 0.126$, Fig. 4a). In contrast, the drug was found to have a significant impact on patient's survival (more severely ill) in the NYC cohort. In comparison to the non-treated group, patients who received carvedilol had a significantly better survival ($p = 0.001$, Fig. 4b).

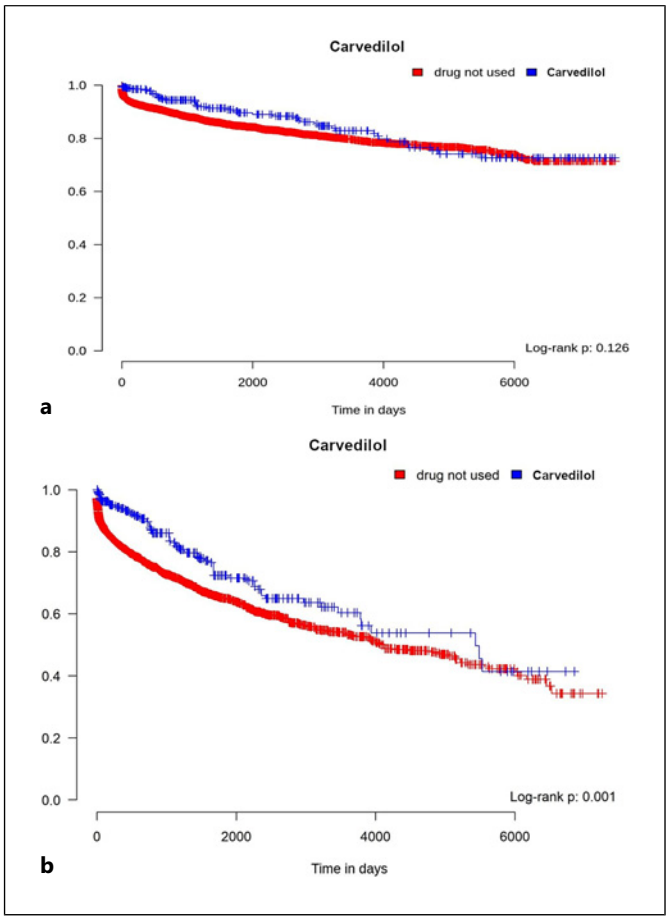
Just as for metoprolol, effects of carvedilol were not observed in female patients with ALD (NYC $p = 0.679$, AUSOM $p = 0.520$, online suppl. Fig. 4). As for male patients, carvedilol had a significant impact on more severely

Downloaded from http://karger.com/ddi/article-pdf/41/5/780/3995630/000529914.pdf by Universitätsbibliothek Heidelberg user on 23 October 2024



Color version available online

Fig. 3. ALD patient's survival. **a** AUSOM cohort treated with metoprolol (blue line) and non-treated (red line). **b** NYC cohort treated with metoprolol (blue line) and non-treated patients (red line).



Color version available online

Fig. 4. ALD patient's survival. **a** AUSOM cohort treated with carvedilol (blue line) and non-treated (red line). **b** NYC cohort treated with metoprolol (blue line) and non-treated patients (red line).

ill patients in NYC (p = 0.000), whereas in the AUSOM cohort, significance evaluation of treatment impact closely missed the 5% error margin (p = 0.075, online suppl. Fig. 4).

Catecholamines: Dopamine and Dobutamine

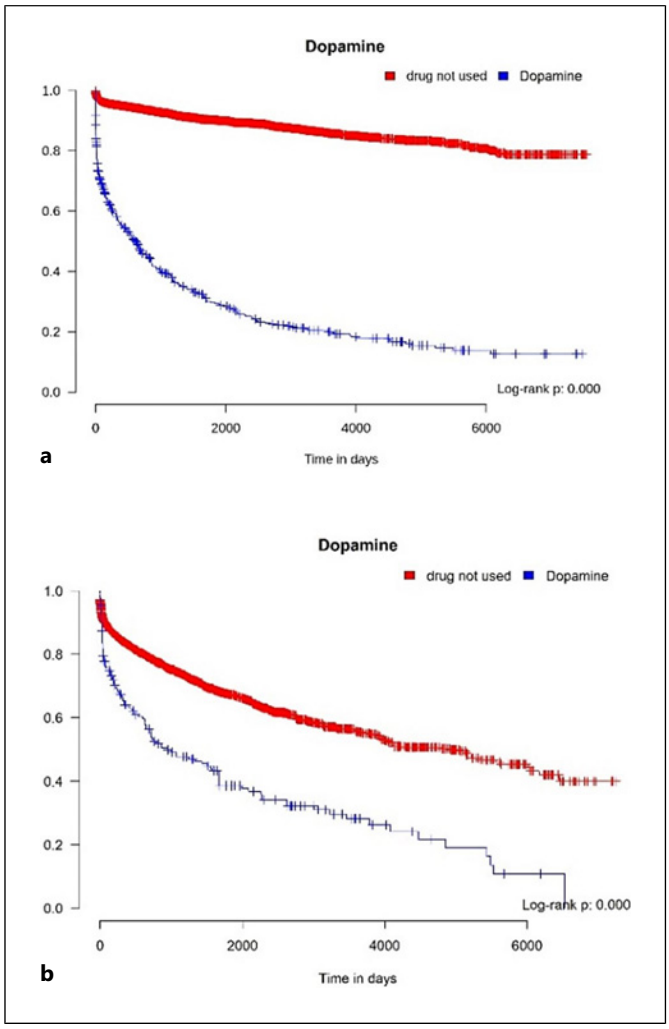
For both AUSOM and NY cohorts, survival rates were low once those patients required treatment with catecholamines. As for dopamine treatment, AUSOM patient's survival rate drops rapidly, advocating for a significant impact on survival probability. Of note, however, an almost steady low plateau of patient's survival was reached in this cohort (p = 0.000, Fig. 5a). In contrast, survival dropped continuously in the NYC dopamine group, again with a significantly increased risk of those patients being treated with dopamine (p = 0.000, Fig. 5b).

Similar results were observed for dobutamine treatment. AUSOM patient's survival rate dropped rapidly before reaching a plateau, showing a highly significant difference in survival (p = 0.000, Fig. 6a). In contrast, survival dropped continuously in the NYC dopamine group, again with a significantly increased risk of those patients being treated with dopamine (p = 0.000, Fig. 6b).

Discussion

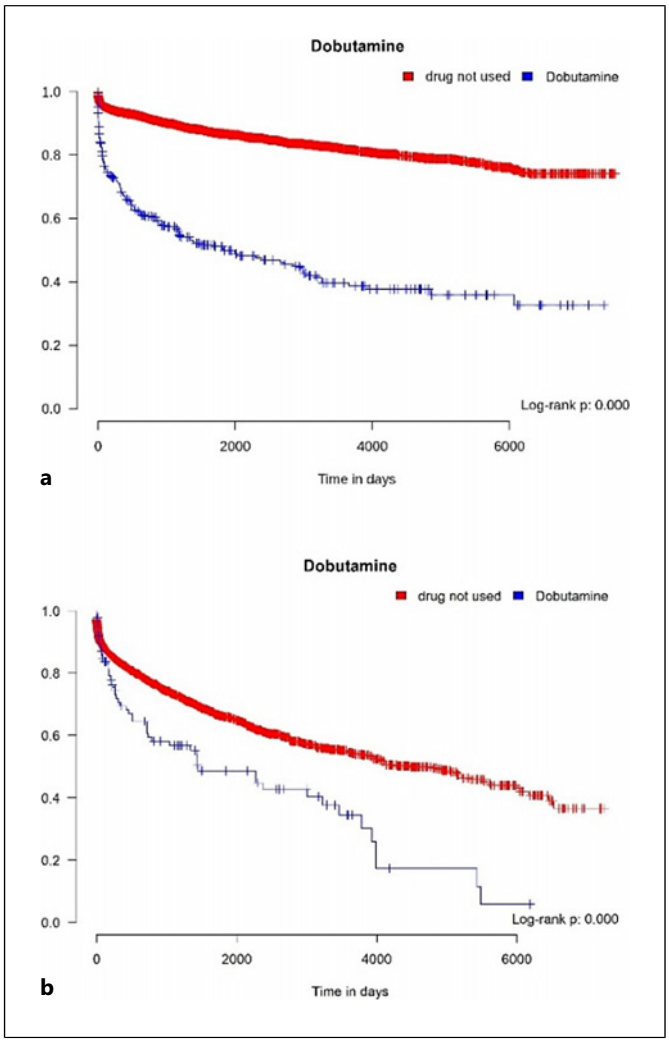
Excessive alcohol consumption leads to a wide spectrum of alcohol-associated liver diseases including alcoholic hepatitis, (acute-on-chronic) liver failure, or liver cirrhosis including its subsequent complications such as portal hypertension or HCC [1, 5]. Due to the severe complications of ALD on personal life, but also a

Downloaded from http://karger.com/ddi/article-pdf/41/5/780/3995630/000529914.pdf by Universitätsbibliothek Heidelberg user on 23 October 2024



Color version available online

Fig. 5. ALD patient's survival. **a** AUSOM cohort treated with dopamine (blue line) and non-treated (red line). **b** NY cohort treated with dopamine (blue line) and non-treated patients (red line).



Color version available online

Fig. 6. ALD patient's survival. **a** AUSOM cohort treated with dobutamine (blue line) and non-treated (red line). **b** NYC cohort treated with dobutamine (blue line) and non-treated patients (red line).

considerable impact on public health and even health economics, it is urgent to identify novel perspectives and treatment options aside from healthy habits and/or abstinence. During the past decade, solid data were accumulated supporting metformin, ASA, or β-blockers as effective drugs in patients with liver cirrhosis, at least to significantly reduce the incidence of HCC or variceal bleeding in patients at risk [4]. However, long-term, real-world data on these drugs and their relevance in patients with ALD are lacking.

Metformin was likely the most prominent drug to be investigated for its protective effect in liver cirrhosis and particularly liver cancer development. Systematic reviews and meta-analyses by Zhou et al. [6] and Decensi et al. [7] both suggested a strong protective association between metformin and HCC risk. However, metformin was also reported to be associated with increased risks of mortality and cirrhotic decompensation in patients with compensated liver cirrhosis [8]. In this context and somewhat in contrast to the data by Yen et al. [8] from Taiwan (although not all of our patients suffered from liver cirrhosis), our data from two large independent cohorts provide important real-world evidence that metformin is of highly significant benefit in both Western and Asian cohorts of chronic ALD. Of note, the benefit was even higher in more severe disease NYC cohort with 63% of patients suffering from liver cirrhosis, a considerable 32.1% reporting ascites, and an additional 18.8% having a history of GI bleeding.

Downloaded from http://karger.com/ddi/article-pdf/41/5/780/3995630/000529914.pdf by Universitätsbibliothek Heidelberg user on 23 October 2024

Also, during the past decade, there is evidence for a protective role of ASA in early liver disease patients and those at risk of HCC development [9–11]. In a recent study based on nationwide Swedish registries, the protective impact of ASA in patients with viral hepatitis demonstrated an estimated cumulative HCC incidence of 4.0% for the ASA group and 8.3% for the non-ASA group within the observation period of 7.9 years. Similar results were found in a Taiwan nationwide cohort study [9]. Also, pooled analysis of 2 prospective US healthcare cohorts even suggested a dose- and duration-dependent benefit in a healthy population. A significantly lower HCC risk was observed with increasing the duration of the use of 1.5 or more standard-dose ASA tablets (325 mg) per week for 5 or more years [10, 12]. In this context, our data clearly demonstrated that indeed ASA can confer protection to those ALD patients.

Non-selective beta-blockers (NSBBs) are well established for prevention of esophageal varices and bleeding [13]. However, not all NSBBs proved equal. Carvedilol, which exhibits additional vasodilatory anti-alfa-1-adrenergic activity, might be deleterious in decompensated patients as it is more likely to cause a systemic hemodynamic depressive effect and may be best avoided or very closely monitored [14]. We therefore investigated both metoprolol and carvedilol for their impact on survival of ALD patients. Surprisingly, effects of both drugs were only significant in male patients, the reason of which remained unclear. For carvedilol, significant effects were only observed in the NYC cohort. This may have to do with the fact that in the AUSOM cohort, only 44.8% of the patients suffered from liver cirrhosis, and it must therefore be assumed that only a minority of patients had portal hypertension which would benefit from β-blocker therapy. Furthermore, it was previously discussed whether the mortality rate of patients with liver cirrhosis may increase as a result of NSBB and therapy-refractory ascites [15–18]. Our data indicate that β-blocker treatment in patients with ascites (not necessarily treatment refractory) may be safe as for both metoprolol and carvedilol treatment, a significant survival advantage was particularly demonstrated in the NYC cohort, including 32% of patients with ascites.

Lastly, catecholamines such as dopamine and dobutamine were discussed to prevent cirrhotic and aberrant liver events due to their roles in ionotropic support [19]. However, our results do not support such a beneficial view on dopamine or dobutamine in ALD patient's survival. This may most likely be due to a strong selection bias as those patients who received catecholamines at one point during their course of disease may usually receive these drugs during ICU treatment. Since the necessity of ICU treatment in ALD patients may per se be a predictor for worse outcome, we believe to basically have selected patients with some sort of ICU treatment requiring severe deterioration of their disease.

As the discussion on catecholamine effects on patient's survival in ALD and a potential selection bias may already indicate, our study also has limitations. Due to the retrospective nature of the register data, we were not able to fully distinguish between compensated and decompensated liver cirrhosis. However, looking at the patient's characteristics as provided in Table 1, we analyzed an NYC cohort with 18.79% GI bleeding, 15.92% encephalopathy, and 32.1% ascites, whereas the South Korean cohort included only 9.32% GI bleeding, 0.69% encephalopathy, and 8.76% ascites. Thus, one could at least argue that the South Korean cohort should mostly suffer from compensated cirrhosis, whereas the NYC group included a considerable number of patients with signs of decompensated liver cirrhosis. Despite this limitation, most results on drug efficacy in cirrhosis were still overlapping between those 2 patient cohorts. Furthermore, for most of the investigated drugs, the exact biochemical mode of action has not yet been clarified. Metformin treatment is still a matter of debate among experts in the field. However, some clinical guidelines (e.g., the recently revised German guideline [20]) already recommend considering treatment in patients with chronic liver disease and non-insulin-dependent diabetes mellitus as it may be considered to reduce the risk of HCC. The authors argued that it is known that the risk of HCC in diabetics, particularly when they suffer from co-existing metabolic syndrome, is increased and a number of publications, mostly retrospective cohort studies, have demonstrated a reduction in the incidence of HCC in diabetics on metformin therapy. In contrast, therapy with metformin in diabetes and chronic liver disease does not necessarily lead to an increased risk of toxicity including the risk of lactic acidosis if well-established contraindications are respected. Overall, our data add considerably to this ongoing discussion by providing further real-world data on two large patient cohorts in favor of metformin treatment and demonstrating an effect on survival.

Conclusion

Overall, our data fill a large gap in long-term, real-world data in patients with ALD. We demonstrated an impact of metformin, ASA, and β-blockers on ALD patient's survival. The need of catecholamines was associated with poor prognosis. However, it became also clear – by performing a comparative analysis of Western and Asian cohorts – that

Downloaded from http://karger.com/ddi/article-pdf/41/5/780/3995630/000529914.pdf by Universitätsbibliothek Heidelberg user on 23 October 2024

not all approaches seemed to be universally applicable. Particularly, gender-specific differences were obvious as, e.g., female Asian patients did not benefit from ASA or NSBB. NSBB treatment was particularly beneficial for the more severely sick patients within the NYC cohort. As the benefit of supportive treatments may vary significantly in Western and Asian cohorts but also among male and female patients, these subgroup analyses will be essential for further, prospective studies.

Statement of Ethics

The need for informed consent was waived by the Columbia University Institutional Review Board, approval number AAAO-7805, last approved March 22, 2022. At Ajou University, the study was approved by the Institutional Review Board, approval number AJOUIRB-MDB-2021-635.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was supported by the Foundation for Biomedical Alcohol Research, Schriesheim, Germany. AT received grants from the Sino-German Center for Research Promotion (GZ-1546 and C-0012).

AT and MPE received funding from the State Ministry of Baden-Wuerttemberg for Sciences, Research and Arts supporting the Clinical Cooperation Unit Healthy Metabolism at the Center for Preventive Medicine and Digital Health and the Baden-Wuerttemberg Center for Digital Early Disease Detection and Prevention (BW-ZDFP). This study also received a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (Grant No. HR16C0001).

Author Contributions

Timo Itzel: data analysis; Thomas Falconer: data curation of NYC cohort and analysis, Ana Roig, Jimmy Daza and Isabella Wiest: data analysis and manuscript preparation; Jimyung Park and Jae Youn Cheong: data collection from Ajou University; Rae Woong Park: data collection and curation from Ajou university; Matthias P. Ebert: manuscript preparation and expert review; George Hripcsak: data framework and data curation of NYC cohort; Andreas Teufel: experimental design, data analysis, and manuscript preparation

Data Availability Statement

All data generated or analyzed during this study are available through the Observational Health Data Sciences and Informatics (OHDSI, see above). Further inquiries can be directed to the corresponding author.

References

1 Subramaniyan V, Chakravarthi S, Jegasothy R, Seng WY, Fuloria NK, Fuloria S, et al. Alcohol-associated liver disease: a review on its pathophysiology, diagnosis and drug therapy. Toxicol Rep. 2021;8:376–85.
2 Crabb DW, Im GY, Szabo G, Mellinger JL, Lucey MR. Diagnosis and treatment of alcohol-associated liver diseases: 2019 practice guidance from the American association for the study of liver diseases. Hepatology. 2020 Jan;71(1):306–33.
3 Kong LZ, Chandimali N, Han YH, Lee DH, Kim JS, Kim SU, et al. Pathogenesis, early diagnosis, and therapeutic management of alcoholic liver disease. Int J Mol Sci. 2019 Jun 2;20(11):2712.
4 Kusnik A, Hunter N, Rasbach E, Miethke T, Reissfelder C, Ebert MP, et al. Co-medication and nutrition in hepatocellular carcinoma: potentially preventative strategies in hepatocellular carcinoma. Dig Dis. 2021;39(5):526–33.
5 Siddiqui MT, Amin H, Garg R, Chadalavada P, Al-Yaman W, Lopez R, et al. Medications in type-2 diabetics and their association with liver fibrosis. World J Gastroenterol. 2020 Jun 21;26(23):3249–59.
6 Zhou YY, Zhu GQ, Liu T, Zheng JN, Cheng Z, Zou TT, et al. Systematic review with network meta-analysis: antidiabetic medication and risk of hepatocellular carcinoma. Sci Rep. 2016 Sep 19;6:33743.
7 Decensi A, Puntoni M, Goodwin P, Cazzaniga M, Gennari A, Bonanni B, et al. Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. Cancer Prev Res. 2010 Nov;3(11):1451–61.
8 Yen FS, Huang YH, Hou MC, Hwu CM, Lo YR, Shin SJ, et al. Metformin use and cirrhotic decompensation in patients with type 2 diabetes and liver cirrhosis. Br J Clin Pharmacol. 2022 Jan;88(1):311–22.
9 Lee TY, Hsu YC, Tseng HC, Yu SH, Lin JT, Wu MS, et al. Association of daily aspirin therapy with risk of hepatocellular carcinoma in patients with chronic hepatitis B. JAMA Intern Med. 2019 May 1;179(5):633–40.
10 Simon TG, Henson J, Osganian S, Masia R, Chan AT, Chung RT, et al. Daily aspirin use associated with reduced risk for fibrosis progression in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2019 Dec;17(13):2776–84 e4.
11 Memel ZN, Arvind A, Moninuola O, Philpotts L, Chung RT, Corey KE, et al. Aspirin use is associated with a reduced incidence of hepatocellular carcinoma: a systematic review and meta-analysis. Hepatol Commun. 2021 Jan;5(1):133–43.
12 Simon TG, Duberg AS, Aleman S, Chung RT, Chan AT, Ludvigsson JF. Association of aspirin with hepatocellular carcinoma and liver-related mortality. N Engl J Med. 2020 Mar 12;382(11):1018–28.
13 European Association for the Study of the Liver Electronic address easloffice@easloffice.eu; European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 2018 Aug;69(2):406–60.
14 Reiberger T, Mandorfer M. Beta adrenergic blockade and decompensated cirrhosis. J Hepatol. 2017 Apr;66(4):849–59.

Downloaded from http://karger.com/ddi/article-pdf/41/5/780/3995630/000529914.pdf by Universitätsbibliothek Heidelberg user on 23 October 2024

15 Mandorfer M, Bota S, Schwabl P, Bucsics T, Pfisterer N, Kruzik M, et al. Nonselective beta blockers increase risk for hepatorenal syndrome and death in patients with cirrhosis and spontaneous bacterial peritonitis. Gastroenterology. 2014 Jun;146(7):1680–90.e1.
16 Serste T, Melot C, Francoz C, Durand F, Rautou PE, Valla D, et al. Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites. Hepatology. 2010 Sep;52(3):1017–22.
17 Leithead JA, Rajoriya N, Tehami N, Hodson J, Gunson BK, Tripathi D, et al. Non-selective beta-blockers are associated with improved survival in patients with ascites listed for liver transplantation. Gut. 2015 Jul;64(7):1111–9.
18 Mookerjee RP, Pavesi M, Thomsen KL, Mehta G, Macnaughtan J, Bendtsen F, et al. Treatment with non-selective beta blockers is associated with reduced severity of systemic inflammation and improved survival of patients with acute-on-chronic liver failure. J Hepatol. 2016 Mar;64(3):574–82.
19 Bernal W, Karvellas C, Saliba F, Saner FH, Meersseman P. Intensive care management of acute-on-chronic liver failure. J Hepatol. 2021 Jul;75(Suppl 1):S163–77.
20 Voesch S, Bitzer M, Blodt S, Follmann M, Freudenberger P, Langer T, et al. S3-Leitlinie: Diagnostik und Therapie des hepatozellulären Karzinoms und biliärer Karzinome – Version 2.0 – Juni 2021, AWMF-Registernummer: 032-053OL. Z Gastroenterol. 2022 Jan;60(1):e131–85.

Downloaded from http://karger.com/ddi/article-pdf/41/5/780/3995630/000529914.pdf by Universitätsbibliothek Heidelberg user on 23 October 2024