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# Safety of Empagliflozin in Patients with Type 2 Diabetes Mellitus in Saudi Arabia: A Post-Authorisation Safety Study

**Saud Alsifri[1*], Abdulrahman M. Almaghamsi[2], Ashraf S. Mahfouz[3], Walid Shehab-Eldin[4], Sameh Rakha[5]**

[1]Endocrinology and Diabetes Department, Alhada Armed Forces Hospital, Taif, Saudi Arabia
[2]Endocrinology and Diabetes Department, King Fahad Medical City, Riyadh, Saudi Arabia
[3]Diabetes Control Center, GNP Hospital, Jeddah, Saudi Arabia
[4]Internal Medicine Department, Saudi-German Hospital Aseer, Khamis Mushait, Saudi Arabia
[5]Medical Department, Boehringer Ingelheim, Riyadh, Saudi Arabia
Email: *saudnafa@hotmail.com

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## Abstract

***Background***: Empagliflozin, a sodium-glucose co-transporter-2 (SGLT2) inhibitor is used as a monotherapy or in combination for lowering the elevated blood glucose level in patients with type 2 diabetes mellitus (T2DM). It is often associated with certain adverse reactions (urinary tract infection (UTI), diabetes ketoacidosis (DKA), and genital infections). Thus, the Saudi Food and Drug Administration requested a post-authorisation safety study to monitor the safety of empagliflozin during the defined observation period. ***Methodology***: The local, comparator, non-interventional, regulatory post-marketing study using "new user" design was conducted in patients with T2DM, treated with empagliflozin (10 or 25 mg) and dipeptidyl peptidase-4 (DPP-4) inhibitors (NCT03764631). Study was conducted from 2018 to 2020, wherein each patient was followed up for 12 months after the index period. Incidence and occurrence of DKA, severe UTIs, volume depletion and dehydration were observed along with metformin, insulin and treatment complexity status and adverse events in the index and Ramadan period. All data collected were analysed using descriptive statistics. ***Results***: Among the 1502 patients enrolled (empagliflozin [n = 751] and DPP-4 inhibitors [n = 751]), 0.1% patients (n = 1) in each group and <1% patients (n = 13) (0.8% [n = 6]: empagliflozin group; 0.9% [n = 7]: DPP-4 inhibitor group) reported the incidence of DKA and volume depletion, respectively. No severe UTIs or dehydration was evident in either group in the index period. No patients reported T2DM-associated complications during the Ramadan period. Metformin, insulin, and treatment com-

plexity status were also evaluated during the study. Overall, 8.1% of patients (n = 121) reported adverse events in the index period while only 0.3% of patients (n = 4) reported adverse events during the Ramadan period. Comparable decline in mean glycated haemoglobin, and no major change in vital signs, along with 81.3% of patients (n = 1221) confirming concomitant medications were noted. ***Conclusion***: Empagliflozin was well tolerated over a period of 12 months, with no safety concerns and a favourable benefit/risk ratio.

## Keywords

Type 2 Diabetes Mellitus, Diabetes Ketoacidosis, Dehydration, Urinary Tract Infection, Volume Depletion, Ramadan, SGLT2 Inhibitor, Saudi Arabia

## 1. Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common chronic metabolic disorders affecting people within the age group of 20 to 79 years, with a global prevalence rate of 9.3% [1] [2]. According to the International Diabetes Federation report, 537 million people are currently living with diabetes worldwide, while 73 million people are affected in the Middle East and North Africa region, with adult prevalence rate in Saudi Arabia being 17.7% [3]. Saudi Arabia has the second-highest prevalence of T2DM in the Middle East and stands seventh in terms of global prevalence. It represents a major public health concern due to associated high levels of morbidity and mortality [4] [5] [6] [7] [8].

Diabetes mellitus is characterised by elevated levels of blood glucose, attributable to the malfunctioning of the feedback loops between insulin action and insulin secretion, thereby culminating into a metabolic imbalance [2]. Pharmacological interventions for T2DM have witnessed a paradigm shift from conventional biguanides (metformin), thiazolidinediones and insulin secretagogues (sulphonylureas and meglitinide analogues) to novel sodium-glucose co-transporter type 2 (SGLT2) inhibitors, incretin mimetics (dipeptidyl peptidase-4 [DPP-4] inhibitors, and glucagon-like peptide 1 receptor agonists) [9] [10] [11]. However, the cornerstone of T2DM management is lifestyle modification, exercise, cessation of smoking, healthy diet and weight management [12].

An important drug category for T2DM used in the recent past is SGLT2 inhibitors that act by diminishing the blood glucose level via partial blockage of glucose reabsorption from the kidney back to the bloodstream, thereby improving the diabetes control [1]. It is also evident that SGLT2 inhibitors improve the renal and cardiovascular outcomes [13]. Several studies have reported that SGLT2 inhibitors are well tolerated and exhibit dose-dependent effectiveness, particularly empagliflozin [1] [14] [15] [16] [17] [18]. Empagliflozin is being widely used as a monotherapy or as an add-on combination therapy; however, it is associated with certain adverse events (AEs) such as urinary tract infection (UTI), diabetic ke-

toacidosis (DKA) and hypoglycaemia [17] [19] [20] [21]. Based on its safety and effectiveness profile, the use of empagliflozin could be paramount during the Ramadan period as this period showcases the aggravation of several risk factors in patients with T2DM, including hypoglycaemia, hyperglycaemia, DKA, dehydration and thrombosis [10] [22].

Therefore, parallel to the launch of SGLT2 inhibitors in Saudi Arabia, post-authorisation safety study (PASS) was conducted upon the request of Saudi Food and Drug Authority (SFDA) to monitor the safety aspects of empagliflozin in patients with T2DM.

## 2. Patients and Methods

### 2.1. Study Design and Participant Selection

This local, comparator, non-interventional, regulatory post-marketing study was conducted to monitor the safety of empagliflozin in patients with T2DM. "New users" design was used wherein comparison was made between empagliflozin (10 or 25 mg) versus DPP-4 inhibitors. A total of 25 sites participated in the study, of which only 18 sites enrolled a total of 1502 patients. The details of the study sites have been incorporated in supplementary **Table S1**. The study was conducted from 2018 to 2020; each patient was followed up for 12 months after the index period, inclusive of Ramadan period. The inclusion criteria for patients in both groups, namely empagliflozin and DPP-4 inhibitors, were primary diagnosis of T2DM performed in Saudi Arabia, having signed informed consent form, at least 18 years of age at the index period, not used other SGLT2 or DPP-4 inhibitors during the previous 12 months of the index period. The exclusion criteria included known hypersensitivity or contraindication to empagliflozin or DPP-4 inhibitor, or any other excipient and the patient being prescribed fixed dose combination (FDC) of SGLT2 inhibitors with DPP-4 inhibitors.

Index period was defined as the date on which each identified new user received the index prescription for empagliflozin or DPP-4 inhibitor.

Ramadan period was defined as the first day of Ramadan to 29$^{th}$ day of Ramadan based on the Islamic Hijri calendar; for 2019: 05 May to 04 Jun. 2019 (±1 to 2 days); for 2020: 23 Apr to 23 May 2020 (±1 to 2 days).

### 2.2. Ethical Considerations

The ethics committee approval was obtained from the Medical Services General Directorate, Research and Ethics Committee, Western Region, Saudi Arabia for 23 sites out of 25 (IRB Registration No. H-02-T-078). One site was approved by IRB, King Fahad Medical Centre (IRB Registration No. H-01-R-012) while another site was approved by Research Center, International Medical Center (IRB Registration No. 2018-12-102). The study was conducted in accordance with the Declaration of Helsinki. The patients signed the informed consent form before enrolling in the study. The study was conducted in accordance with the laws, regulations, and relevant guidelines of Saudi Arabia. (NCT03764631)

### 2.3. Methodology

All patients were followed up for 12 months after the index period (inclusive of Ramadan period) or until any of the specified conditions were met (death, specific exclusion criteria, the last continuous treatment of the index drug [empagliflozin or DPP-4 inhibitor], or new treatment episode started with any of the other index drugs). All the patients attended 4 follow-up visits at baseline, Week 16 ± 2, Week 32 ± 2 and Week 52. The investigators assessed and recorded the preliminary study parameters such as medical history, glycated haemoglobin (HbA1c), blood glucose level, renal functions, physical examinations, concomitant mediations, comorbidities, prior medication exposure, AEs, hospitalisation, etc. at successive visits, wherever applicable, into the electronic case report forms.

The incidence and time of first occurrence of DKA, severe UTI, volume depletion and dehydration were the primary outcomes and were evaluated in the index period (Diabetes ketoacidosis is defined as a serious complication of diabetes characterised by high level of ketones in the body due to lack of insulin and low food intake; severe UTI is defined as pyelonephritis or urosepsis; volume depletion is defined as the reduction in the extracellular fluids; and dehydration is defined as the loss of total body water that leads to hypertonicity). The secondary outcomes were diabetes-associated complications evaluated during the Ramadan period. Metformin, insulin, and treatment complexity status, along with analysis of AEs were conducted across both the treatment groups at the index and follow-up period along with Ramadan period.

### 2.4. Analysis

The sample size of 1500 patients was planned as per the SFDA requirements; as per regulations to detect DKA, 750 patients need to be enrolled in each group. Propensity scores were used for the quantitative analysis of probability of receiving empagliflozin at the index date for new users of both empagliflozin and DPP-4 inhibitors. Sensitivity analysis was performed to evaluate potential bias and confounding. The data collected were represented as arithmetic means, standard deviations (SDs), medians, minimum and maximum values for continuous data and confidence intervals (CI), wherever applicable. All statistical tests were conducted with a 2-sided significance level $\alpha$ of 0.05 and analysis was performed using statistical analysis software (SAS®) version 9.4.

## 3. Results

### 3.1. Study Population

Overall, 1502 patients were enrolled in the study, of which 93.7% (n = 1408) completed 1 year of treatment and their treatment status was still ongoing at the end of study. Of the remaining patients, 5.7% (n = 86) terminated the study early due to loss to follow-up (4.9%, n = 74); switching of treatment (0.4%, n = 6); AE-related termination (0.1%, n = 1); and reasons not specified (0.3%, n = 5). The data were unavailable for 0.5% of patients (n = 8) after completion of 1 year

of treatment.

Overall, 64.2% (n = 965) of the enrolled patients were male and the mean age of the enrolled patients at index date was 52.5 ± 10.5 years (Table 1). The overall median duration of T2DM at index period was 53 months and more than 60% (n = 982) of the patients had a family history of T2DM. The most common medical condition across both the groups was metabolism and nutritional disorders (36.6%, n = 550), followed by vascular disorders (20.3%, n = 305) (with respect to System Organ Class [SOC]), while hypertension (20%, n = 301) followed by hyperlipidaemia (14.6%, n = 220) and dyslipidaemia (11.9%, n = 178) were the primary conditions as per the preferred term [PT]). More than 90% of the patients reported no prior insulin use. The mean HbA1c, fasting blood glucose (FBG), complete blood count (CBC), liver function tests, renal function parameters and lipid profile were comparable across the 2 treatment groups. Majority of the patients (81.3%, n = 1221) were on prior medications, with 77.8% (n = 1168) being on anti-hyperglycaemic agents and 19.5% on lipid-modifying agents (19.5%, n = 293).

### 3.2. Primary Outcomes

Only 0.1% (n = 1) of patient in both the treatment groups reported the occurrence of DKA; the first occurrence in the index period in the empagliflozin and the DPP-4 inhibitor groups was 365 days and 344 days, respectively. However, 0.8% (n = 6) patients in the empagliflozin group and 0.9% (n = 7) patients in the DPP-4 inhibitor group (total: <1%, n = 13) exhibited the occurrence of volume depletion; the time to first occurrence in the index period in empagliflozin and DPP-4 inhibitor groups was 169 ± 131 days and 256.1 ± 110.5 days, respectively. The treatment-adjusted incidence rate ratio of DKA and volume depletion in empagliflozin/DPP-4 inhibitors groups was 0.981 and 0.841, respectively (Table 2). None of the patients reported the occurrence of UTI and dehydration across both treatment groups. Similar result was observed in the follow-up period.

### 3.3. Secondary Outcomes

None of the patients in the 2 treatment groups had the incidence of DKA, severe UTI, volume depletion or dehydration in the index and follow-up periods during Ramadan.

### 3.4. Metformin Status at Baseline

Out of 751 patients in each treatment group, 271 patients in the empagliflozin group and 331 patients in the DPP-4 inhibitors group were on metformin FDC therapy at baseline. The occurrence of DKA in those on metformin was reported by 0.4% and 0.3% (n = 1 in each case) of patients in the empagliflozin and DPP-4 inhibitor groups, respectively. Out of the 13 patients (<1%) reporting volume depletion, 1.1% (n = 3) were on empagliflozin and 1.2% (n = 4) were on DPP-4 inhibitor; metformin was used as FDC in both cases at baseline (Table 3). None of the patients on metformin FDC at baseline reported the incidence of

DKA in the index period. No patients across both the treatment groups reported the incidence of severe UTI or dehydration in the index period. Similar results were obtained during the follow-up period.

**Table 1.** Patient demographics.

| Parameter | Empagliflozin (N = 751) | DPP-4 Inhibitors (N = 751) | Total (N = 1502) |
|---|---|---|---|
| Age at index date (years) | | | |
| Mean | 52.1 | 52.9 | 52.5 |
| SD | 10.3 | 10.7 | 10.5 |
| Median | 52 | 53 | 52.5 |
| Minimum | 21 | 21 | 21 |
| Maximum | 80 | 92 | 92 |
| <30 | 6 (0.8) | 5 (0.7) | 11 (0.7) |
| 30 to 64 | 663 (88.3) | 645 (85.9) | 1308 (87.1) |
| >64 | 82 (10.9) | 101 (13.4) | 183 (12.2) |
| Gender, n (%) | | | |
| Male | 478 (63.6) | 486 (64.8) | 965 (64.2) |
| Female | 273 (36.4) | 264 (35.2) | 537 (35.8) |

Abbreviation: DPP-4: Dipeptidyl peptidase-4.

**Table 2.** Incidence of diabetic ketoacidosis and volume depletion in the index period.

| Parameters | Empagliflozin (N = 751) | DPP-4 Inhibitors (N = 751) | Rate Ratio |
|---|---|---|---|
| ***Incidence of DKA*** | | | |
| Patients with events in the period, n (%) | 1 (0.1) | 1 (0.1) | |
| Patients without event, n (%) | 750 (99.9) | 750 (99.9) | |
| Crude incidence rate | 0.001 | 0.001 | 1 |
| (95% confidence interval) | 0 (0.007) | 0 (0.007) | |
| Treatment-adjusted incidence rate | | | |
| (crude per 1000 patient-years) | 1.380 | 1.407 | 0.981 |
| (95% confidence interval) | (0.035, 7.690) | (0.036, 7.842) | |
| ***Incidence of volume depletion*** | | | |
| Patients with events in the period, n (%) | 6 (0.8) | 7 (0.9) | |
| Patients without event, n (%) | 745 (99.2) | 744 (99.1) | |
| Crude incidence rate | 0.008 | 0.009 | 0.889 |
| (95% confidence interval) | (0.003, 0.017) | (0.004, 0.019) | |
| Treatment-adjusted incidence rate | | | |
| (crude per 1000 patient-years) | 8.282 | 9.852 | 0.841 |
| (95% confidence interval) | (3.04, 18.03) | (3.96, 20.30) | |

Abbreviation: DKA: Diabetic ketoacidosis; DPP-4: Dipeptidyl peptidase-4. Note: The mean ± SD duration of the index period and follow-up period was 350.6 ± 66.7 days and 351 ± 65.7 days, respectively. Crude incidence rate is the proportion of patients with events in the respective period.

**Table 3.** Incidence of diabetic ketoacidosis and volume depletion in index period by metformin status.

| Parameters | Empagliflozin (N = 271) | DPP-4 Inhibitors (N = 331) | Rate Ratio |
|---|---|---|---|
| *Incidence of DKA with metformin* | | | |
| Patients with events in the period, n (%) | 1 (0.4) | 1 (0.3) | |
| Crude incidence rate | 0.004 | 0.003 | 1.333 |
| (95% confidence interval) | (0, 0.020) | (0, 0.017) | |
| Treatment-adjusted incidence rate (crude per 1000 patient-years) | 1.380 | 1.407 | 0.981 |
| (95% confidence interval) | (0.035, 7.690) | (0.036, 7.842) | |
| *Incidence of volume depletion with metformin* | | | |
| Patients with events in the period, n (%) | 3 (1.1) | 4 (1.2) | |
| Patients without event, n (%) | 268 (98.9) | 327 (98.8) | |
| Crude incidence rate | 0.011 | 0.012 | 0.917 |
| (95% confidence interval) | (0.002, 0.032) | (0.003, 0.031) | |
| Treatment-adjusted incidence rate (crude per 1000 patient-years) | 4.141 | 5.630 | 0.736 |
| (95% confidence interval) | (0.854, 12.101) | (1.534, 14.415) | |
| Time from start of period to first occurrence in period (days) | 76.7 ± 15 | 225 ± 137.9 | |
| | **Empagliflozin (N = 480)** | **DPP-4 Inhibitors (N = 420)** | **Rate Ratio** |
| *Incidence of volume depletion without metformin* | | | |
| Patients with events in the period, n (%) | 3 (0.6) | 3 (0.7) | |
| Patients without event, n (%) | 477 (99.4) | 417 (99.3) | |
| Crude incidence rate | 0.006 | 0.007 | 0.857 |
| (95% confidence interval) | (0.001, 0.018) | (0.001, 0.021) | |
| Treatment-adjusted incidence rate (crude per 1000 patient-years) | 4.141 | 4.222 | 0.981 |
| (95% confidence interval) | (0.854, 12.101) | (0.871, 12.340) | |
| Time from start of period to first occurrence in period (days) | 261.3 ± 130.8 | 297.7 ± 60 | |

Abbreviation: DKA: Diabetic ketoacidosis; DPP-4: Dipeptidyl peptidase-4.

None of the patients across both treatment groups had the incidence of DKA, UTI, volume depletion and dehydration in the index and follow-up periods during Ramadan.

### 3.5. Treatment Complexity Status at Baseline

The patients in each treatment group were divided based on the treatment complexity status: on mono glucose-lowering drug (GLD) treatment (empagliflozin group: 116 patients; DPP-4 inhibitor group: 113 patients), dual GLD treatment (empagliflozin group: 343 patients; DPP-4 inhibitor group: 393 patients), triple

GLD treatment (empagliflozin group: 231 patients; DPP-4 inhibitor group: 209 patients), quadruple GLD treatment (empagliflozin group: 43 patients; DPP-4 inhibitor group: 29 patients), quintuple GLD treatment (empagliflozin group: 12 patients; DPP-4 inhibitor group: 6 patients), sextuple GLD treatment (empagliflozin group: 4 patients; DPP-4 inhibitor group: 1 patients), septuple GLD treatment (empagliflozin group: 1 patient; DPP-4 inhibitor group: 0 patients) and octuple GLD treatment (empagliflozin group: 1 patient; DPP-4 inhibitor group: 0 patients).

It was reported that 2.3% (n = 1) and 0.3% patients (n = 1) reported DKA in the empagliflozin group and DPP-4 inhibitor groups while being on quadruple GLDs and dual GLDs therapy, respectively, at the baseline. All 13 patients (<1%) reporting volume depletion was on GLD combinations at baseline (dual, triple, quadruple, and quintuple (Table 4). None of the patients in either of the 2 treatment groups had the incidence of severe UTI or dehydration in the index period. Similar results were reported in the follow-up period.

None of the patients in 2 treatment groups had the incidence of DKA, severe UTI, volume depletion or dehydration in the index and follow-up periods during Ramadan.

Table 4. Incidence of diabetic ketoacidosis and volume depletion in index period by glucose-lowering drug status.

| *Incidence of DKA in Index Period by GLD Status—Dual Treatment* | | | |
|---|---|---|---|
| | **Empagliflozin (N = 343)** | **DPP-4 Inhibitors (N = 393)** | **Rate Ratio** |
| Patients with events in the period, n(%) | 0 | 1 (0.3) | |
| Crude incidence rate | 0 | 0.003 | 0 |
| (95% confidence interval) | (0, 0.011) | (0, 0.014) | |
| Treatment-adjusted incidence rate | | | |
| (crude per 1000 patient-years) | 0 | 1.407 | 0 |
| (95% confidence interval) | (0, 5.092) | (0.036, 7.842) | |
| *Incidence of DKA in Index Period by GLD Status—Quadruple Treatment* | | | |
| | **Empagliflozin (N = 43)** | **DPP-4 Inhibitors (N = 29)** | **Rate Ratio** |
| Patients with events in the period, n (%) | 1 (2.3) | 0 | |
| Crude incidence rate | 0.023 | 0 | |
| (95% confidence interval) | (0.001, 0.123) | (0.000, 0.119) | |
| Treatment-adjusted incidence rate | | | |
| (crude per 1000 patient-years) | 1.380 | 0.000 | |
| (95% confidence interval) | (0.035, 7.690) | (0, 5.192) | |
| *Incidence of Volume Depletion in Index Period by GLD Status—Dual Treatment* | | | |
| | **Empagliflozin N = 343** | **DPP-4 Inhibitors N = 393** | **Rate Ratio** |
| Patients with events in the period, n (%) | 2 (0.6) | 5 (1.3) | |
| Patients without event, n (%) | 341 (99.4) | 388 (98.7) | |

**Continued**

| | | | |
|---|---|---|---|
| Crude incidence rate | 0.006 | 0.013 | 0.462 |
| (95% confidence interval) | (0.001, 0.021) | (0.004, 0.029) | |
| Treatment-adjusted incidence rate | | | |
| (crude per 1000 patient-years) | 2.761 | 7.037 | 0.392 |
| (95% confidence interval) | (0.334, 9.972) | (2.285, 16.423) | |
| Time from start of period to first occurrence in period (days) | 229 ± 190.9 | 287 ± 75.6 | |
| ***Incidence of Volume Depletion in Index Period by GLD Status—Triple Treatment*** | | | |
| | **Empagliflozin N = 231** | **DPP-4 Inhibitors** N = 209 | **Rate Ratio** |
| Patients with events in the period, n (%) | 2 (0.9) | 1 (0.5) | |
| Patients without event, n (%) | 229 (99.1) | 208 (99.5) | |
| Crude incidence rate | 0.009 | 0.005 | 1.800 |
| (95% confidence interval) | (0.001, 0.031) | (0.000, 0.026) | |
| Treatment-adjusted incidence rate | | | |
| (crude per 1000 patient-years) | 2.761 | 1.407 | 1.962 |
| (95% confidence interval) | (0.334, 9.972) | (0.036, 7.842) | |
| Time from start of period to first occurrence in period (days) | 187 ± 168.3 | 309 | |
| ***Incidence of Volume Depletion in Index Period by GLD Status—Quadruple Treatment*** | | | |
| | **Empagliflozin N = 43** | **DPP-4 Inhibitors** N = 29 | **Rate Ratio** |
| Patients with events in the period, n (%) | 0 | 1 (3.4) | |
| Crude incidence rate | 0 | 0.034 | 0 |
| (95% confidence interval) | (0, 0.082) | (0.001, 0.178) | |
| Treatment-adjusted incidence rate | | | |
| (crude per 1000 patient-years) | 0 | 1.407 | 0 |
| (95% confidence interval) | (0, 5.092) | (0.036, 7.842) | |
| ***Incidence of Volume Depletion in Index Period by GLD Status—Quintuple Treatment*** | | | |
| | **Empagliflozin N = 12** | **DPP-4 Inhibitors** N = 6 | **Rate Ratio** |
| Patients with events in the period, n (%) | 2 (16.7) | 0 | |
| Patients without event, n (%) | 10 (83.3) | 6 (100) | |
| Crude incidence rate | 0.167 | 0 | |
| (95% confidence interval) | (0.021, 0.484) | (0, 0.459) | |
| Treatment-adjusted incidence rate | | | |
| (crude per 1000 patient-years) | 2.761 | 0 | |
| (95% confidence interval) | (0.334, 9.972) | (0, 5.192) | |
| Time from start of period to first occurrence in period (days) | 91 ± 32.5 | | |

Abbreviation: DKA: Diabetic ketoacidosis; DPP-4: Dipeptidyl peptidase-4; GLD: Glucose-lowering drugs.

### 3.6. Insulin Use at Baseline

The primary outcomes were evaluated based on the use of insulin at baseline, wherein 50 patients in the empagliflozin group and 26 patients in the DPP-4 inhibitors group confirmed the usage.

The occurrence of DKA was reported in 2% of the patients (n = 1) in the empagliflozin group using insulin and 0.1% (n = 1) of the patient on DPP-4 inhibitor without insulin at baseline. Out of the 13 patients (<1%) reporting volume depletion, only 2% of the patients (n = 1) in the empagliflozin group confirmed the use of insulin (Supplementary Table S2). None of the patients in the 2 treatment groups had the incidence of severe UTI or dehydration in the index period. Similar results were reported in the follow-up period.

None of the patients in the 2 treatment groups had the incidence of DKA, severe UTI, volume depletion or dehydration in the index and follow-up periods during Ramadan.

### 3.7. Adverse Event Summary

Overall, 8.1% (n = 121) of patients reported AEs, wherein 7.7% of patients (n = 58) were treated with empagliflozin and 8.4% of the patients (n = 63) with DPP-4 inhibitor in the index period. A total of 0.3% of the patients (n = 4) reported AEs in the index period during Ramadan, where 0.4% (n = 3) were from the empagliflozin group and 0.1% (n = 1) was treated with DPP-4 inhibitors. A detailed representation of different types of AEs is provided in Table 5.

Table 5. Classification of different adverse events observed.

| | Empagliflozin (N = 751) | DPP-4 Inhibitors (N = 751) | Total (N = 1502) |
|---|---|---|---|
| Number (%) of patients | | | |
| with any AE | 58 (7.7) | 63 (8.4) | 121 (8.1) |
| with any severe AE | 2 (0.3) | 1 (0.1) | 3 (0.2) |
| with any SAE | 6 (0.8) | 2 (0.3) | 8 (0.5) |
| with any designated SAE | 2 (0.3) | 2 (0.3) | 4 (0.3) |
| hospitalised | 6 (0.8) | 1 (0.1) | 7 (0.5) |
| hospitalised with any AESI | 1 (0.1) | 1 (0.1) | 2 (0.1) |
| Number (%) of deaths | 0 | 0 | 0 |
| Number (%) of patients discontinuing study due to AE | 0 | 1 (0.1) | 1 (0.1) |
| Number (%) of patients discontinuing treatment due to AE | 1 (0.1) | 2 (0.3) | 3 (0.2) |
| *In the Index Period during Ramadan* | | | |
| Number (%) of patients with any AE | 3 (0.4) | 1 (0.1) | 4 (0.3) |

Abbreviation: AE: Adverse event; AESI: Adverse event of special interest; DPP-4: Dipeptidyl peptidase-4; SAE: Serious adverse event. Note: The mean ± SD duration of the index period and follow-up period during Ramadan was 30.8 ± 3.0 days.

#### 3.7.1. In Relation to SOC and PT

On further analysis based on the SOC and PT in the index period, maximum events reported were gastrointestinal disorders (26 events), followed by nervous system disorders (23 events) and general disorders and administration (20 events). With respect to PT, none of the AEs were present in >1% of the patients in the 2 treatment groups. In the index period during Ramadan, a total of 0.3% (n = 4) patients reported 4 AEs, where 0.4% (n = 3) of patients in the empagliflozin group reported 3 AEs (infections and infestations [corona virus infection], metabolism and nutrition disorder [hypoglycaemia] and renal and urinary disorder [chromaturia] [1 patient each]) and 0.1% (n = 1) patient in the DPP-4 inhibitors group reported 1 AE (gastrointestinal disorder [nausea]).

#### 3.7.2. Incidence of AEs in Relation to Study Treatment

A total of 8 empagliflozin-related AEs were observed in 1.1% of patients (n = 8) (hypoglycaemia: 3; thirst: 2; fungal infection: 2; genital fungal infection:1). However, most of these events were mild, except for 1 event each of hypoglycaemia and fungal infection. During the Ramadan period, 0.4% (n = 1) patient reported 1 empagliflozin-related hypoglycaemia.

#### 3.7.3. Incidence of Adverse Events of Special Interest

A total of 0.3% of patients (n = 4) reported 5 adverse events of special interest (AESIs) in the index period (empagliflozin group: 0.1% [n = 1] patient each of DKA and UTI; DPP-4 inhibitor group: 0.1% [n = 1] patient reported DKA, 0.1% [n = 1] patient reported 1 event each of acute kidney injury and end-stage renal disease).

#### 3.7.4. Serious Adverse Events

A total of 0.5% (n = 8) of patients reported 10 serious AEs (SAEs) in the index period, where 6 patients were from the empagliflozin group, and 2 patients were from the DPP-4 inhibitor group. Of 6 patients reporting 7 SAEs in the empagliflozin group, 1 patient each reported 1 SAE of myocardial ischaemia, anal fissure, hernia, DKA and obesity, and 1 patient reported 2 SAEs (pneumonia and lung adenocarcinoma). Of the 2 patients treated with DPP-4 inhibitor, 3 SAEs were reported (1 patient reported 1 event of DKA and another patient reported 2 SAEs [acute kidney injury and end-stage renal disease]).

### 3.8. Other Variables

Comparable decline was reported in mean HbA1c levels from baseline to visits 2, 3 and 4 in both treatment groups. No major changes were observed in mean weight, body mass index, pulse rate, systolic blood pressure and diastolic blood pressure across different visits. A total of 8.3% patients (n = 1221) affirmed using concomitant medication, primarily anti-hyperglycaemic medications (empagliflozin group: 82.8% [n = 622]; DPP-4 inhibitor group: 79.8% [n = 599]), followed by lipid-modifying agents (empagliflozin group: 20.1% [n = 151]; DPP-4 inhibitor group: 20% [n = 150]); and agents acting on renin-angiotensin system (em-

pagliflozin group: 14.2% [n = 105]; DPP-4 inhibitor group: 12.3% [n = 92]). Similar results were reported in the index and follow-up periods during Ramadan.

## 4. Discussion

Previous clinical studies have established the safety and effectiveness of SGLT2 inhibitors in significantly improving the glycaemic control along with exhibiting a well-tolerated safety profile [1] [14] [23] [24] [25] [26] [27]. The pharmacokinetic and exposure-response studies of empagliflozin substantiated no significant change in the risk of UTI, hypoglycaemia or volume depletion [15] and a well-documented favourable benefit-risk profile was established [28]. Empagliflozin has been incorporated as an add-on to metformin therapy and as monotherapy, it is well tolerated in both cases [19] [21] [29]. However, certain studies have shed light on hypoglycaemic AEs, UTIs and volume depletion across treatment groups using SGLT2 during different studies [21] [30].

The association of T2DM with DKA was established in 41.4% of the patients with T2DM in a hospital-based retrospective analysis, thereby highlighting the risk factor in patients with T2DM [31]. A separate study presented DKA as a major concern in using SGLT2, where hospitalisation was observed in 4 patients, thereby reinforcing the need to establish the safety profile of these medications [32]. It was studied that DKA is prevalent in almost one-third of the patients presenting with T2DM, causing an increase in the hospitalisation and economic burden [33] [34]. In a post-authorisation safety and effectiveness study of dapagliflozin in Saudi Arabia, 12.3% of the patients with T2DM reported the AEs, with UTI and DKA at 1% and 0.2% of all the events, respectively [14]. Another paramount concern in patients with T2DM is UTI that warrants a routine urine analysis. It was established that patients with T2DM more than 40 years of age and female patients in particular are at a higher risk of asymptomatic UTI, although the overall prevalence of UTI in T2DM is nearly 11.5% [35] [36] [37] [38]. A retrospective analysis of tofogliflozin, an SGLT2 inhibitor, exhibited significant glucose-lowering competencies with low associated risk of electrolyte abnormalities and dehydration [39]. Ertugliflozin, an SGLT2 inhibitor, did not lead to significant volume depletion (1.2% - 1.9%; dose-dependent) as reported in the randomised double-blind trial [40]. The key trends observed in the current study using empagliflozin were in corroboration with the previously published clinical evidence, where less than 1% of the patients reported T2DM-associated complications (0.1% patients [n = 1] reported DKA each from empagliflozin and DPP-4 inhibitor group; <1% patients reported volume depletion across both the groups). None of the patients reported UTI or dehydration. Thus, the obtained results reinforced the safety profile of empagliflozin.

The medical ramifications of fasting during Ramadan are still unexplored. However, because of the fasting in patients with T2DM, insulin secretion is perturbed, resulting in T2DM-associated complications such as hypoglycaemia, hyper-

glycaemia, DKA, dehydration and thrombosis along with a significant lowering in the blood lipid profile, blood pressure, HbA1c level [10] [22] [41]. A meta-analysis reported that there was an improvement in the HbA1c and hypoglycaemic control when patients with T2DM were treated with SGLT2 during Ramadan, with no major AEs [42]. The DIA-RAMADAN, a real-world study and VIRTUE study evaluated the safety profile of anti-diabetic treatment during the Ramadan period which reported reductions in HbA1c, weight control and fasting plasma glucose [22] [43]. The outcome of the present study with empagliflozin confirmed that none of the patients reported any incidence of DKA, UTI, volume depletion or dehydration during the Ramadan period, which was in line with the established literature.

Thus, the present study provides insights on the safety aspect of empagliflozin, an SGLT2 inhibitor, which was exhibited to be safe during the 1-year period in Saudi Arabia, parallel to its launch in the region. However, we do acknowledge certain limitations of the study. The incidences of DKA, severe UTI, volume depletion and dehydration were not analysed across different age groups, male versus female, duration of disease and varying doses of study treatment. The sample size was determined as per the SFDA requirement, which could be received as limited considering the anticipated incidences of outcomes. Laboratory investigations (CBC, lipid profile, and liver and renal function tests) were not performed for subsequent visits, which further limited the assessment of the impact of study treatment on laboratory parameters.

The strength of the study lies in the fact that it brings out the safety data specific to Saudi Arabia for empagliflozin in patients with T2DM as a regulatory mandate. Furthermore, a PASS for T2DM encompassing and comparing the diabetes-associated complications in the index period and Ramadan period in a single study is practically unavailable. Thus, this study might form a foundation for future follow-up studies on an elaborate scale to yield more profound outcomes.

## 5. Conclusion

The study evinced empagliflozin in reducing blood glucose levels in patients with T2DM in Saudi Arabia when administered as per the local prescribing information. The outcome was also evaluated during the Ramadan period when all the safety and tolerability parameters were adequately met. Overall, no safety concerns were recognised during the study, thereby underpinning the favourable benefit/risk ratio of empagliflozin. Currently, no update on the empagliflozin prescribing information is deemed necessary. Nonetheless, extensive follow-up studies are warranted to address the study limitations and further complement the study outcomes.

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## Disclosure

Dr. Sameh Rakha is the employee of Boehringer Ingelheim.

## Data Availability Statement

Data are available on request due to privacy/ethical restrictions. The data that support the findings of this study are available on request from the corresponding author, Dr. Saud Alsifri. The data are not publicly available due to restrictions (containing information that could compromise the privacy of research participants).

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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**Supplementary Table S1.** Details of study sites.

| S.no. | Type of study site | Investigator name | Site address |
|---|---|---|---|
| 1 | Active | Dr. Saud Nafa M Alsifri | Al Hada Armed Forces Hospital , AlHada Moutain, Post Box 1347, Taif 21944, SAU |
| 2 | Active | Dr. Essa Moharib Aldhafiri | Alalam Medical Center, Khalid Bin Alwaleed St Khalid Ibn Al Walid Street, Al Quds, P.O.Box: 60581, Riyadh 13214, SAU |
| 3 | Active | Dr. Mohamed Abdalhameed A. Albhoshi | Alansari Specialist Hospital, Umm Al Qura Road, P.O.Box: 30894, Yanbu 46455, SAU |
| 4 | Active | Dr. Thaseena Khaliq | Al Abeer Medical Center, Aziziyah Branch, 7730 Hijazi Al Adawi, Al Aziziyah District -2720 Jeddah 23342 7730, SAU. |
| 5 | Active | Dr. Ehab Mahmoud Osman Ali | Saudi German Hospital, Batterjee Road P.O.Box: 2550, Jeddah 21461, SAU |
| 6 | Active | Dr. Abdulrahman Mohammed Al Maghamsi | Obesity, Endocrine and Metabolism Center King Fahad Medical City, P.O. Box. 59046, Riyadh 11525, SAU |
| 7 | Active | Dr. Hany Abdelbary Elbasyouny | Prince Fahad bin Sultan hospital, Sultanah, P.O.Box:1626, Tabuk 47311, SAU |
| 8 | Active | Dr. Saeed Abdelwhab Afify | Shifa Hospital, Al Mansour Street, P.O.Box: 2322, Makkah 24232, SAU |
| 9 | Active | Dr. Fathima Bushra Hasan | DAFA Special Polyclinic, Al Samer District, P.O.Box: 12887, Jeddah 21214, SAU |
| 10 | Active | Dr. EmadElDin Mohammed Khairy | Al Amal Medical Group, KSA Yanbu Royal Commission Al semeri, P.O.Box: 30530, Yanbu 46455, SAU |
| 11 | Active | Dr. Ashraf Shaaban Mahfoez | Ghassan Najeeb Pharaon Hospital, Prince Sultan Street, P.O.Box 4553, Jeddah 21412, SAU |
| 12 | Active | Dr. Talaat Sayed Ahmed Allisy | Abha International Private Hospital, Imam Mohammed Bin Saud Road, P.O.Box: 1794, Abha 61431, SAU |
| 13 | Active | Dr. Ali Akbar TP | Al Abeer Polyclinic, Bawadi Branch, P.O.Box: 52868, Jeddah 23531, SAU |
| 14 | Active | Dr. Salah Fuaad MOHD Al Sayd | Al Rahman Polyclinic, Al Rasaifah, P.O.Box: 9178, Makkah 24232, SAU |
| 15 | Active | Dr. Khalid Sayedi | Abha International Private Hospital, Imam Mohammed Bin Saud Road, P.O.Box: 1794, Abha 61431, SAU |
| 16 | Active | Dr. Huda Mustafa Khader Dahbour | Al Zafer Hospital, King Abdulaziz Rd, Najran 66261, Saudi Arabia. |
| 17 | Active | Dr. Walid Abdelmohsen Shehab Eldin | Saudi German Hospital, 10, King Fahd Road Al-Hijlah District, Aseer 62451, Saudi Arabia |
| 18 | Terminated | Dr. Hamzeh Irshaid Alarqan | International Medical Center, Hayel Street, Jeddah 21451, SAU |
| 19 | Non recruiting | Dr. Diaa Mansour Ewis | Saudi German Hospital, Batterjee Road P.O.Box: 2550, Jeddah 21461, SAU |
| 20 | Non recruiting | Dr. Mohammed Azizullah | Al-Abeer Medical Center, Sharafiyah branch, P.O.Box: 52868, Jeddah 21573, SAU |
| 21 | Non recruiting | Dr. Mohamed A. Agag | Riyadh Medical Center, Oruba, Post Box 50768, Riyadh 11533, SAU |
| 22 | Non recruiting | Dr. Khaled Abdullah Abdulrahman Tayeb | Al-Noor Specialist Hospital, Kudai, P.O.Box: 6251, Makkah 24241, SAU |
| 23 | Non recruiting | Dr. Yasser S. Sheta | Dr.Bakhsh Hospital, P.O.Box: 6940 Jeddah 21452, SAU |
| 24 | Non recruiting | Dr. Abdulrahman Abdulmohsen AlShaikh | Dr. Soliman Fakeeh Hospital, Falastin ‹Al-Hamra'a, P.O.Box: 2537, Jeddah 21461, SAU |
| 25 | Non recruiting | Dr. Oussama Mohamad Nimr Khatib | Mouwasat Hospital, P.O. Box 3399 Khobar 34234, Alkhobar, Saudi Arabia |

**Supplementary Table S2.** Incidence of DKA and volume depletion in index period by insulin status.

| *Incidence of DKA in Index Period by Insulin—Yes* | | | |
|---|---|---|---|
| | **Empagliflozin (N = 50)** | **DPP-4 Inhibitors (N = 26)** | **Rate Ratio** |
| Patients with events in the period, n(%) | 1 (2) | 0 | |
| Crude incidence rate | 0.020 | 0 | |
| (95% confidence interval) | (0.005, 0.135) | (0.868, 1) | |
| Treatment-adjusted incidence rate | | | |
| (crude per 1000 patient-years) | 1.380 | 0 | 0 |
| (95% confidence interval) | (0.035, 7.690) | (0, 5.192) | |
| *Incidence of DKA in Index Period by Insulin Status—No* | | | |
| | **Empagliflozin (N = 701)** | **DPP-4 Inhibitors (N = 725)** | **Rate Ratio** |
| Patients with events in the period, n (%) | 0 | 1 (0.1) | |
| Crude incidence rate | 0 | 0.001 | 0 |
| (95% confidence interval) | (0.995, 1.000) | (0, 0.010) | |
| Treatment-adjusted incidence rate | | | |
| (crude per 1000 patient-years) | 0 | 1.407 | |
| (95% confidence interval) | (0, 5.092) | (0.036, 7.842) | |
| *Incidence of Volume Depletion in Index Period by Insulin Status—Yes* | | | |
| | **Empagliflozin N = 50** | **DPP-4 Inhibitors N = 26** | **Rate Ratio** |
| Patients with events in the period, n (%) | 1 (2) | 0 | |
| Crude incidence rate | 0.002 | 0 | 0 |
| (95% confidence interval) | (0.005, 0.135) | (0.868, 1.000) | |
| Treatment-adjusted incidence rate | | | |
| (crude per 1000 patient-years) | 1.380 | 0 | 0 |
| (95% confidence interval) | (0.035, 7.690) | (0, 5.192) | |
| *Incidence of Volume Depletion in Index Period by Insulin Status—No* | | | |
| | **Empagliflozin N = 701** | **DPP-4 Inhibitors** N = 725 | **Rate Ratio** |
| Patients with events in the period, n (%) | 5 (0.7) | 7 (1.0) | |
| Patients without event, n (%) | 696 (99.3) | 718 (99.0) | |
| Crude incidence rate | 0.007 | 0.010 | 0.700 |
| (95% confidence interval) | (0.002, 0.017) | (0.004, 0.020) | |
| Treatment-adjusted incidence rate | | | |
| (crude per 1000 patient-years) | 6.901 | 9.852 | 0.700 |
| (95% confidence interval) | (2.241, 16.105) | (3.961, 20.299) | |
| Time from start of period to first occurrence in period (days) | 180 ± 143.4 | 256.1 ± 110.5 | |

Abbreviation: DKA: Diabetic ketoacidosis; DPP-4: Dipeptidyl peptidase-4.

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# Comparison of Child-Pugh, MELD, MELD-Na, and ALBI Scores in Predicting In-Hospital Mortality in Patients with HCC

**Yun Liu[1*], Lijian Ran[1*], Hongjia Zhang[1], Heling Ren[2], Xin Jiang[2], Pinliang Liao[2#], Min Ou[2#]**

[1]Department of Gastroenterology, Southwest Hospital, The First Affiliated Hospital of Army Medical University, Chongqing, China
[2]Department of Cardiovascular Medicine, Southwest Hospital, The First Affiliated Hospital of Army Medical University, Chongqing, China
Email: #oumin1522342@sina.com, #tomyliao@126.com

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## Abstract

**Background & Objectives:** Hepatocellular carcinoma (HCC) leads to high morbidity and mortality. Various models have been proposed for predicting the outcome of patients with HCC. We aim to compare the prognostic abilities of Child-Pugh, MELD, MELD-Na, and ALBI scores for predicting in-hospital mortality of HCC. **Methods:** We enrolled patients diagnosed with liver cirrhosis and HCC from May 2017 through May 2018. We further divided eligible patients into hepatitis B virus (HBV), patients without ascites, and patients with ascites subgroups. Areas under the characteristic curves (AUCs) were analyzed. **Results:** A total of 495 patients were included in the study. We collected data on patients at admission. A majority of patients were infected with HBV (91.5%). None of them were complicated with hepatic encephalopathy. Only 14.9% of patients presented with ascites. In the whole population, AUCs with 95% confidence interval (CI) of Child-Pugh, ALBI, MELD, and MELD-Na scores in predicting in-hospital mortality were 0.889 (95% CI: 0.858 - 0.915), 0.849 (95% CI: 0.814 - 0.879), 0.669 (95% CI: 0.626 - 0.711), and 0.721 (95% CI: 0.679 - 0.760), respectively. In the patients without ascites subgroup, Child-Pugh showed better discriminatory ability than ALBI score in predicting in-hospital mortality (P = 0.0002), while there were no significant differences among other comparisons. **Conclusions:** Child-Pugh and ALBI may be useful predictors for predicting in-hospital mortality in whole patients, in patients with HBV infection, and in patients without ascites. In HCC patients with ascites, MELD-Na may be effective for predicting in-hospital mortality.

*Authors contributed equally to the paper.
#Corresponding authors.

**Keywords**

Hepatocellular Carcinoma, Child-Pugh Score, MELD Score, MELD-Na Score, ALBI Score, In-Hospital Mortality

## 1. Introduction

Hepatocellular carcinoma (HCC) is the fourth cause of cancer-related mortality all over the globe [1]. HCC is the second leading cause of cancer disability-adjusted life-years (DALYs), which increases the disease burden of patients [2]. Chronic hepatitis B virus (HBV) and hepatitis C infection (HCV) infection are the primary causes of HCC. Approximately 85% - 95% of patients with HCC are in the setting of liver cirrhosis concerning viral hepatitis infection [3]. With an increasing incidence of obesity, diabetes, and metabolic syndrome in developed regions, non-alcoholic steatohepatitis (NASH) has become the predominant risk factor for HCC [4] [5]. Alcohol abuse, aflatoxin B1, and aristolochic acid exposure also contributed to the occurrence of HCC [6] [7] [8]. Chronic viral hepatitis infection may progress to liver cirrhosis or HCC even when they achieve sustained virological response (SVR). Moreover, there is no approved therapy for NASH [9] [10]. Therefore, early identification of high-risk populations is crucial for improving the prognosis and reducing the disease-related mortality and health burden of HCC patients.

The Child-Pugh score, including five variables, total bilirubin, albumin, ascites, hepatic encephalopathy (HE), and international normalized ratio (INR), has been widely used for assessing liver function. However, subjective indicators may reduce its reliability [11]. The model for end-stage liver diseases (MELD), calculated by total bilirubin, creatinine, and INR, has been used for evaluating patients who should undergo liver transplantation in priority, which substantially reduces mortality [12]. Serum sodium (Na) has been reported as an independent predictor associated with liver-related complications and mortality [13] [14]. MELD-Na, incorporating Na into the MELD algorithm, shows more accuracy decreasing waiting list mortality than MELD [15]. It also has been validated in patients with HBV infection, liver cirrhosis, acute-on-chronic hepatitis B liver failure (HBV-AoCLF), HCC, and patients undergoing transjugular intrahepatic portosystemic shunt (TIPS) and liver transplantation [16]-[22]. Albumin-bilirubin score (ALBI), including two objective parameters, albumin and bilirubin, which eliminates the subjective inclination of HE and ascites in Child-Pugh, has been used for assessing the prognosis in patients with HCC, liver cirrhosis, and HBV-AoCLF [23] [24] [25]. Previous studies have compared the accuracy of various invasive tools in evaluating the prognosis of patients with HCC, whereas the results turn out to be different [18] [26] [27]. Our study aims to explore the discriminatory abilities among Child-Pugh, MELD, MELD-Na, and ALBI scores in predicting in-hospital mortality of patients with liver cirrhosis complicated with HCC.

## 2. Material and Methods

### 2.1. Patients and Methods

We retrospectively collected patients admitted to Southwest Hospital between May 2017 and May 2018. All patients were diagnosed with liver cirrhosis and HCC based on medical history, imaging, or histopathological examinations. Patients with other malignancies and incomplete laboratory results were excluded. In-hospital mortality was defined as an outcome. STARD reporting guidelines were applied [28].

The following characteristics included etiology, serum biomarkers at admission (red blood count, platelets, total bilirubin, albumin, creatinine, Na, K, Ca, INR, etc.), patients presenting with HE and ascites, and in-hospital death were reviewed. Child-Pugh, MELD, MELD-Na, and ALBI scores were calculated. We further analyzed patients with HBV infection, with or without ascites. This study was approved by the Ethics Committee Board of Southwest Hospital (KY2021009).

Child-Pugh was calculated based on five parameters: total bilirubin, albumin, ascites, HE, and INR. Grade A: 5 - 6 scores; grade B: 7 - 9 scores; grade C: 10 - 15 scores.

MELD [12] = 9.57 × loge (creatinine (mg/dL) + 3.78 × loge (bilirubin (mg/dL)) + 11.2 × loge (INR) + 6.43

MELD-Na [16] = MELD + 1.59 × (135 − Na (mmol/L))

ALBI [23] = 0.66 × log10 (bilirubin (μmol/L)) − 0.085 × (albumin (g/L))

ALBI is classified into three grades: grade 1 ≤ −2.6; grade 2 > −2.6 and ≤ −1.39; grade 3 > −1.39.

### 2.2. Statistical Analysis

Continuous data were expressed as mean ± standard deviation (SD) and median (range). Categorical data were expressed as frequency (percentage). The analysis was performed by SPSS version 23.0. The predictive abilities of the four scores were calculated using the receiver operating characteristic (ROC) curve analyses. The areas under the ROC curves (AUCs) with 95% confidence intervals (CIs) were compared by the De-long test. The cut-off value, sensitivity, specificity, positive likelihood ratio (LR), and negative LR were also shown. ROC analyses were performed by MedCalc version 11.4.2.0. P-value < 0.05 was considered significantly different.

## 3. Results

After exclusion, 495 patients with liver cirrhosis suffering HCC were included in the analysis. The baseline characteristics were shown in **Table 1**. The in-hospital mortality was 1.0% (5/495). A total of 439 patients were male sex (88.7%). The majority of patients were infected with HBV (91.5%), followed by alcohol abuse (3.6%). Most patients did not complicate with ascites (85.1%). None of them presented with HE at admission. The mean value of Child-Pugh, ALBI, MELD, and MELD-Na were 5.6 ± 1.2, −2.5 ± 0.6, 5.5 ± 3.6, and −1.4 ± 6.4, respectively.

**Table 1.** Baseline characteristics.

| Variables | Mean ± SD or Frequency (percentage) | Median (Range) |
|---|---|---|
| Sex (male/female) | 439/56 | |
| Age (years) | 53.8 ± 10.6 | 53.0 (24.0 - 80.0) |
| **Causes of liver diseases, n (%)** | | |
| Hepatitis B virus | 453 (91.5) | |
| Hepatitis C virus | 7 (1.4) | |
| Alcohol | 18 (3.6) | |
| Hepatitis B virus + Alcohol | 3 (0.6) | |
| Hepatitis B virus + Hepatitis C virus | 1 (0.2) | |
| Unknown | 13 (2.6) | |
| **Vital signs** | | |
| Systolic blood pressure (mmHg) | 123.6 ± 15.2 | 122.0 (90.0 - 180.0) |
| Diastolic blood pressure (mmHg) | 78.4 ± 10.8 | 78.0 (50.0 - 114.0) |
| Heart rate (b.p.m.) | 79.0 ± 13.2 | 78.0 (50.0 - 123.0) |
| **Laboratory tests** | | |
| RBC ($10^{*12}$/L) | 4.4 ± 0.7 | 4.5 (1.8 - 6.6) |
| Hb (g/L) | 135.8 ± 22.3 | 140.0 (51.0 - 187.0) |
| WBC ($10^{*12}$/L) | 5.0 ± 2.2 | 4.7 (1.1 - 22.9) |
| PLT ($10^{*9}$/L) | 127.8 ± 75.9 | 117.0 (6.0 - 552.0) |
| TBIL (umol/L) | 27.6 ± 47.6 | 18.1 (4.1 - 483.3) |
| DBIL (umol/L) | 10.4 ± 29.6 | 5.2 (0.8 - 398.2) |
| IBIL (umol/L) | 16.8 ± 22.3 | 12.3 (0.8 - 398.2) |
| ALB (g/L) | 39.6 ± 5.9 | 40.2 (21.7 - 54.2) |
| ALT (U/L) | 55.0 ± 74.3 | 35.2 (3.0 - 893.0) |
| AST (U/L) | 73.3 ± 139.6 | 39.5 (13.4 - 1810.1) |
| ALP (U/L) | 135.9 ± 108.5 | 111.0 (24.0 - 1743.0) |
| GGT (U/L) | 115.9 ± 138.9 | 69.0 (7.0 - 1079.0) |
| BUN (mmol/L) | 5.6 ± 2.0 | 5.2 (2.2 - 18.4) |
| CR (umol/L) | 72.0 ± 16.1 | 71.0 (35.1 - 166.2) |
| K (mmol/L) | 4.0 ± 0.4 | 4.0 (2.8 - 5.8) |
| Na (mmol/L) | 139.4 ± 2.8 | 139.5 (120.0 - 150.0) |
| Ca (mmol/L) | 2.3 ± 0.2 | 2.3 (1.8 - 3.1) |
| PT (second) | 12.8 ± 1.7 | 12.4 (10.0 - 29.1) |
| APTT (second) | 31.5 ± 6.4 | 30.1 (18.9 - 74.8) |
| INR | 1.1 ± 0.1 | 1.1 (0.9 - 2.5) |
| **Ascites (No/Mild/Moderate-Severe)** | 421/51/23 | |
| **Hepatic encephalopathy (No/Grade I-II/Grade III-IV)** | 495/0/0 | |
| **Child-Pugh class (A/B/C)** | 418/69/8 | |
| **Child-Pugh score** | 5.6 ± 1.2 | 5.0 (5.0 - 11.0) |
| **MELD score** | 5.5 ± 3.6 | 5.2 (−3.4 - 25.4) |
| **ALBI grade (1/2/3)** | 249/220/26 | |
| **ALBI score** | −2.5 ± 0.6 | −2.6 (−3.8 - (−0.2)) |
| **MELD-Na score** | −1.4 ± 6.4 | −2.5 (−20.1 - 43.9) |

**Abbreviations**: ALB, albumin; ALBI, albumin-bilirubin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CR, creatinine; DBIL, direct bilirubin; GGT, gamma-glutamyl transpeptidase; IBIL, indirect bilirubin; INR, international normalized ratio; MELD, model for end-stage liver disease; PLT, platelet; PT, prothrombin time; RBC, red blood count; SD, standard deviation; TBIL, total bilirubin; WBC, white blood count.

As presented in Table 2, Child-Pugh showed a good performance in predicting in-hospital mortality. The AUC of Child-Pugh was 0.889 (95% CI: 0.858 - 0.915, P < 0. 0001), with a sensitivity of 100.00% and specificity of 70.20%. The cut-off value was 5. ALBI was also a good discriminator in evaluating in-hospital mortality. The AUC of ALBI was 0.849 (95% CI: 0.814 - 0.879, P < 0. 0001), with a sensitivity of 100.00% and specificity of 72.45%. The cut-off value was −2.22. The AUCs of MELD and MELD-Na were 0.669 (95% CI: 0.626 - 0.711, P = 0.339) and 0.721 (95% CI: 0.679 - 0.760, P = 0.153), respectively. The cut-off values were 10.74 and 3.59, respectively. However, the prognostic differences among the four scores were not statistically significant.

### 3.1. Patients with HBV Infection

We analyzed 453 HCC patients with HBV infection. The baseline characteristics were presented in Table S1. Four patients died in the hospital (0.9%). The mean values of Child-Pugh, ALBI, MELD, and MELD-Na were 5.6 ± 1.1, −2.5 ± 0.6, 5.4 ± 3.5, and −1.5 ± 6.0, respectively. The AUCs of Child-Pugh, ALBI, MELD, and MELD-Na were 0.872 (95% CI: 0.838 - 0.901, P < 0.0001), 0.823 (95% CI: 0.785 - 0.857, P < 0.0001), 0.607 (95% CI: 0.560 - 0.652, P = 0.614), and 0.653 (95% CI: 0.607 - 0.696, P = 0.398), respectively. The results of comparisons among Child-Pugh, ALBI, MELD, and MELD-Na were shown in Figure 1. No statistically significant differences were observed among the comparisons of the four scores (All P values > 0.05).

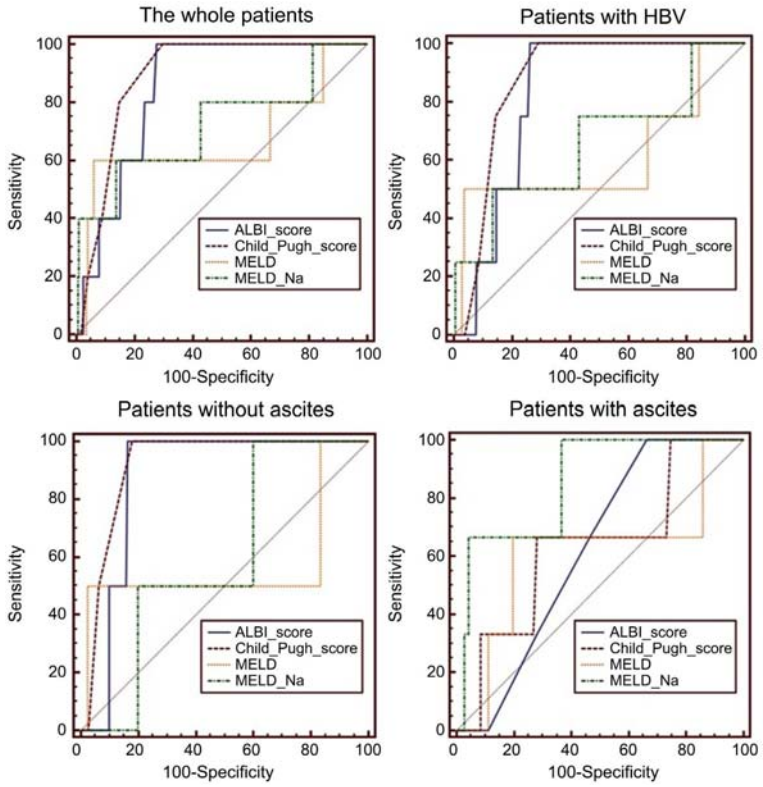


Figure 1. Comparison of four scores.

Table 2. ROC analyses of Child-Pugh, MELD, MELD-Na, and ALBI scores.

| Prognostic scores | AUC (95% CI) | Cut-off value | Sensitivity (95%CI) | Specificity (95% CI) | Positive LR | Negative LR | P value |
|---|---|---|---|---|---|---|---|
| **The whole patients** | | | | | | | |
| Child-Pugh score | 0.889 (0.858 - 0.915) | 5 | 100.00 (47.8 - 100) | 70.20 (65.9 - 74.2) | 3.36 | 0 | <0.0001 |
| ALBI score | 0.849 (0.814 - 0.879) | −2.22 | 100.00 (47.8 - 100) | 72.45 (68.3 - 76.4) | 3.63 | 0 | <0.0001 |
| MELD score | 0.669 (0.626 - 0.711) | 10.74 | 60.00 (14.7 - 94.7) | 93.88 (91.4 - 95.8) | 9.80 | 0.43 | 0.3391 |
| MELD-Na score | 0.721 (0.679 - 0.760) | 3.59 | 60.00 (14.7 - 94.7) | 86.33 (83.0 - 89.2) | 4.39 | 0.46 | 0.1527 |
| **Subgroup—Patients with HBV infection** | | | | | | | |
| Child-Pugh score | 0.872 (0.838 - 0.901) | 5 | 100.00 (39.8 - 100) | 71.05 (66.6 - 75.2) | 3.45 | 0 | <0.0001 |
| ALBI score | 0.823 (0.785 - 0.857) | −2.22 | 100.00 (39.8 - 100) | 73.72 (69.4 - 77.7) | 3.81 | 0 | <0.0001 |
| MELD score | 0.607 (0.560 - 0.652) | 11.36 | 50.00 (6.8 - 93.2) | 96.44 (94.3 - 97.9) | 14.03 | 0.52 | 0.6135 |
| MELD-Na score | 0.653 (0.607 - 0.696) | 3.59 | 50.00 (6.8 - 93.2) | 86.64 (83.1 - 89.6) | 3.74 | 0.58 | 0.3982 |
| **Subgroup—Patients without ascites** | | | | | | | |
| Child-Pugh score | 0.918 (0.887 - 0.942) | 5 | 100.00 (15.8 - 100) | 82.10 (78.1 - 85.7) | 5.59 | 0 | <0.0001 |
| ALBI score | 0.871 (0.835 - 0.901) | −2.16 | 100.00 (15.8 - 100) | 83.77 (79.9 - 87.2) | 6.16 | 0 | <0.0001 |
| MELD score | 0.570 (0.522 - 0.618) | 11.36 | 50.00 (1.3 - 98.7) | 97.61 (95.7 - 98.8) | 20.95 | 0.51 | 0.8623 |
| MELD-Na score | 0.600 (0.552 - 0.647) | −1.59 | 100.00 (15.8 - 100) | 39.86 (35.1 - 44.7) | 1.66 | 0 | 0.6206 |
| **Subgroup—Patients with ascites** | | | | | | | |
| Child-Pugh score | 0.622 (0.502 - 0.732) | 6 | 100.00 (29.2 - 100) | 33.80 (23.0 - 46.0) | 1.51 | 0 | 0.2873 |
| ALBI score | 0.634 (0.514 - 0.743) | −1.63 | 66.67 (9.4 - 99.2) | 71.83 (59.9 - 81.9) | 2.37 | 0.46 | 0.4984 |
| MELD score | 0.610 (0.490 - 0.722) | 10.28 | 66.67 (9.4 - 99.2) | 80.28 (69.1 - 88.8) | 3.38 | 0.42 | 0.6432 |
| MELD-Na score | 0.854 (0.753 - 0.926) | 3.59 | 100.00 (29.2 - 100.0) | 63.88 (51.1 - 74.5) | 2.73 | 0 | 0.0018 |

**Abbreviations**: ALBI, albumin-bilirubin; AUC, area under the receiver operating characteristic curve; CI, confidence interval; HBV, hepatitis B virus; LR, likelihood ratio; MELD, model for end-stage liver disease; ROC, receiver operating characteristic.

### 3.2. Patients Presented without Ascites

To compare the predictive power of the four scores in HCC patients with and without ascites, we did further analysis. In patients without ascites, the in-hospital mortality was 0.5% (2/421). The mean values of Child-Pugh, ALBI, MELD, and MELD-Na scores were 5.3 ± 0.7, −2.6 ± 0.5, 5.1 ± 3.2, and −2.2 ± 5.3, respectively (Table S2). Child-Pugh and ALBI had better discriminatory performance than MELD and MELD-Na in predicting in-hospital mortality in this subgroup. The AUCs of Child-Pugh, ALBI, MELD, and MELD-Na in predicting in-hospital mortality were 0.918 (95% CI: 0.838 - 0.901, P < 0.0001), 0.871 (95% CI: 0.835 - 0.901, P < 0.0001), 0.570 (95% CI: 0.522 - 0.618, P = 0.862), and 0.600 (95% CI: 0.552 - 0.647, P = 0.621), respectively (Table 2). In this subgroup, Child-Pugh showed excellent predictive ability in predicting in-hospital mortality. Furthermore, Child-Pugh was a superior discriminator than ALBI in assessing in-hospital mortality (P = 0.0002). Nevertheless, there were no differences when compared between the other scores (Figure 1).

### 3.3. Patients Presented with Ascites

A total of 74 patients presented with ascites. In this subgroup, three patients occurred death in hospital (4.1%). Fifty-one patients were complicated with mild ascites at admission (68.9%). The mean values of Child-Pugh, ALBI, MELD, and MELD-Na were 7.6 ± 1.4, −1.9 ± 0.6, 7.8 ± 4.5, and 3.1 ± 9.8, respectively, which were higher than those in other groups (**Table S3**). The AUCs of Child-Pugh, ALBI, MELD, and MELD-Na were 0.622 (95% CI: 0.502 - 0.732, P = 0.287), 0.634 (95% CI: 0.514 - 0.743, P = 0.498), 0.610 (95% CI: 0.490 - 0.722, P = 0.643), and 0.854 (95% CI: 0.753 - 0.926, P = 0.002), respectively (**Table 2**). In this subgroup, MELD-Na was the only significant prognostic score in predicting in-hospital mortality. However, no significant differences were found in the comparisons (**Figure 1**).

## 4. Discussion

We performed a retrospective study to compare the predictive abilities of Child-Pugh, ALBI, MELD, MELD-Na in predicting in-hospital mortality of patients with HCC. We found that Child-Pugh and ALBI performed better discriminatory abilities than MELD and MELD-Na except for patients with ascites group. In patients without ascites, Child-Pugh provided significantly better prognostic performance than the ALBI score. In patients with ascites, MELD-Na was superior to the other three scores. MELD has the lowest discriminatory ability in predicting in-hospital mortality in all groups. However, there were no statistically significant differences when compared among the four scores in the whole patients, in HBV infection, and in patients with ascites groups. We may explain these results from the following three aspects.

Firstly, most HCC patients in our hospital are not in severe conditions. None of the patients presents with HE. A few patients develop complications like gastrointestinal bleeding, hepatorenal syndrome, or spontaneous bacterial peritonitis. Child-Pugh and ALBI scores mainly focus on evaluating liver function, whereas MELD and MELD-Na consist of parameters evaluating renal function, which may contribute to the superiority of Child-Pugh and ALBI scores.

Secondly, patients with low sodium levels are prone to develop ascites, which may explain why MELD-Na is superior to the other three scores in patients with ascites subgroup.

Thirdly, the majority of patients are infected with HBV, which conforms with the epidemiology in our country. Although new antiviral medications have been used for clinical application, patients who have progressed to liver cirrhosis or do not receive SVR also have the risk of developing HCC.

Barcelona Clinical Liver Cancer (BCLC) staging system is the most widely used system for HCC staging classification, which could guide therapeutic strategies [29]. Patients with very early stage (0) are the candidates for surgery, and patients with early stage (A) are eligible for liver transplantation, local ablation, or percutaneous ethanol injection. Patients with the intermediate stage (B) are

recommended for chemoembolization and patients with advanced stage (C) are eligible for sorafenib. Patients with the terminal stage (D) should receive supportive care [30]. Unfortunately, nearly half of patients are first diagnosed at an advanced stage, which results in poor prognosis due to lack of curative treatment. Therefore, to reduce the mortality of patients with HCC, it is essential for improving risk stratification and discriminating patients with early stages.

Ultrasonography (US) is the primary tool which is recommended for surveillance of HCC, whereas it can be affected by doctors' experience and obesity. AFP is the most commonly used serum biomarker for the diagnosis and surveillance of HCC but with low sensitivity. It has been reported that des-gamma-carboxyprothrombin (DCP) performs superior diagnostic accuracy than AFP regardless of tumor size, population, and etiology [31]. With the combination of DCP or US could improve the reliability of AFP in detecting early-stage HCC [20]. Previous studies have shown that serum GP73 is an independent factor for assessing complications and predicting postoperative outcomes in HCC patients undergoing hepatectomy [32]. The combinations of miR-130b, miR-150, miR-182, miR-215, and miR-96 are excellent for the diagnosis of HCC, with an accuracy of 94.1%. Promising technologies such as liquid biopsies, including circulating tumor DNA (ctDNA) and circulating cell-free DNA (cfDNA), have been testified useful for detection and surveillance of HCC. However, these new serum biomarkers are not recommended for lacking further validation. Therefore, reliable and effective non-invasive prognosticators for risk stratification of HCC are needed for clinical guidance.

There have been many studies comparing the discriminative abilities of various prognostic biomarkers. Zhao *et al.* conducted a retrospective study enrolling patients with HCC after liver resection, which compared the prognostic values between Child-Pugh and ALBI scores in predicting postoperative overall survival. Results showed that ALBI was superior to Child-Pugh [33]. They also performed a retrospective study including HCC patients who received transarterial chemoembolization (TACE), ALBI also performed better prognostic capability than Child-Pugh in predicting survival [34]. Hiraoka *et al.* also revealed ALBI was preferable to Child-Pugh in assessing liver function in HCC patients [35]. To compare with our study, the opposite results may contribute to patient selection and condition. Kim *et al.* have compared the prognostic performances among Child-Pugh, MELD, MELD-Na, and ALBI scores in HCC patients with ascites. MELD-Na could effectively discriminate liver function and mortality, which was consistent with our results [20]. Except for the above-mentioned non-invasive prognostic scores, new models such as platelet-albumin-bilirubin (PALBI), malnutrition, modified Glasgow prognostic score (mGPS), and neutrophil-to-lymphocyte ratio (NLR) have been reported as independent factors in predicting outcomes of HCC [36] [37] [38] [39]. Nonetheless, these prognostic indicators still need to be validated by well-designed trials before applying them to clinical practice.

There are some limitations in our study that should be mentioned. This was a retrospective study; we could not collect complete data; we did not stratify patients with different HCC stages or patients who received different therapies; no patient included in this study presented with HE; this study lacked long-term follow-up.

## 5. Conclusion

In summary, Child-Pugh and ALBI may be effective predictors for assessing in-hospital mortality in cirrhotic patients complicated with HCC. However, in HCC patients with ascites, MELD-Na may be an alternative indicator for predicting in-hospital mortality. Moreover, new models assessing liver function combined with tumor stages may be more effective for predicting prognosis in HCC patients. Further studies should be strictly designed to explore new prognostic models.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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**Table S1.** Baseline characteristics of patients with HBV infection.

| Variables | Mean ± SD or Frequency (percentage) | Median (Range) |
|---|---|---|
| Sex (male/female) | 401/52 | |
| Age (years) | 53.1 ± 10.5 | 52.0 (24.0 - 77.0) |
| **Vital signs** | | |
| Systolic blood pressure (mmHg) | 123.3 ± 15.2 | 122.0 (90.0 - 180.0) |
| Diastolic blood pressure (mmHg) | 78.6 ± 10.8 | 78.0 (50.0 - 114.0) |
| Heart rate (b.p.m.) | 79.1 ± 13.2 | 78.0 (50.0 - 123.0) |
| **Laboratory tests** | | |
| RBC ($10^{*12}$/L) | 4.5 ± 0.7 | 4.5 (1.8 - 6.6) |
| Hb (g/L) | 136.7 ± 22.0 | 141.0 (51.0 - 187.0) |
| WBC ($10^{*12}$/L) | 5.0 ± 2.2 | 4.7 (1.1 - 22.9) |
| PLT ($10^{*9}$/L) | 130.1 ± 77.3 | 121.0 (6.0 - 552.0) |
| TBIL (umol/L) | 26.3 ± 43.3 | 18.0 (4.1 - 483.3) |
| DBIL (umol/L) | 9.7 ± 27.2 | 5.1 (0.8 - 398.2) |
| IBIL (umol/L) | 16.3 ± 21.1 | 12.3 (0.8 - 314.1) |
| ALB (g/L) | 39.8 ± 5.8 | 40.3 (21.7 - 54.2) |
| ALT (U/L) | 56.1 ± 76.9 | 35.5 (3.0 - 893.0) |
| AST (U/L) | 74.4 ± 145.1 | 39.7 (13.4 - 1810.1) |
| ALP (U/L) | 134.5 ± 112.1 | 108.0 (24.0 - 1743.0) |
| GGT (U/L) | 111.1 ± 138.4 | 65.0 (7.0 - 1079.0) |
| BUN (mmol/L) | 5.5 ± 1.9 | 5.2 (2.2 - 18.4) |
| CR (umol/L) | 71.9 ± 15.9 | 71.0 (35.1 - 166.2) |
| K (mmol/L) | 4.0 ± 0.4 | 4.1 (2.9 - 5.8) |
| Na (mmol/L) | 139.4 ± 2.6 | 139.5 (126.8 - 150.0) |
| Ca (mmol/L) | 2.3 ± 0.1 | 2.3 (1.8 - 2.9) |
| PT (second) | 12.8 ± 1.7 | 12.4 (10.0 - 29.1) |
| APTT (second) | 31.3 ± 6.1 | 30.1 (18.9 - 67.6) |
| INR | 1.1 ± 0.1 | 1.1 (0.9 - 2.5) |
| **Ascites (No/Mild/Moderate-Severe)** | 386/48/19 | |
| **Hepatic encephalopathy (No/Grade I-II/Grade III-IV)** | 453/0/0 | |
| **Child-Pugh class (A/B/C)** | 385/62/6 | |
| **Child-Pugh score** | 5.6 ± 1.1 | 5.0 (5.0 - 11.0) |
| **MELD score** | 5.4 ± 3.5 | 5.1 (−3.4 - 25.4) |
| **ALBI grade (1/2/3)** | 235/196/22 | |
| **ALBI score** | −2.5 ± 0.6 | −2.6 (−3.8 - (−0.2)) |
| **MELD-Na score** | −1.5 ± 6.0 | −2.4 (−20.1 - 38.5) |

**Abbreviations**: ALB, albumin; ALBI, albumin-bilirubin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CR, creatinine; DBIL, direct bilirubin; GGT, gamma-glutamyl transpeptidase; HBV, hepatitis B virus; IBIL, indirect bilirubin; INR, international normalized ratio; MELD, model for end-stage liver disease; PLT, platelet; PT, prothrombin time; RBC, red blood count; SD, standard deviation; TBIL, total bilirubin; WBC, white blood count.

**Table S2.** ROC analyses of Child-Pugh, MELD, MELD-Na, and ALBI scores.

| Variables | Mean ± SD or Frequency (percentage) | Median (Range) |
|---|---|---|
| Sex (male/female) | 374/47 | |
| Age (years) | 53.5 ± 10.6 | 53.0 (24.0 - 80.0) |
| **Causes of liver diseases, n (%)** | | |
| Hepatitis B virus | 386 (91.7) | |
| Hepatitis C virus | 6 (1.5) | |
| Alcohol | 15 (3.5) | |
| Hepatitis B virus + Hepatitis C virus | 1 (0.2) | |
| Unknown | 13 (3.1) | |
| **Vital signs** | | |
| Systolic blood pressure (mmHg) | 124.2 ± 15.1 | 123.0 (90.0 - 180.0) |
| Diastolic blood pressure (mmHg) | 78.9 ± 10.4 | 79.0 (52.0 - 114.0) |
| Heart rate (b.p.m.) | 78.1 ± 12.7 | 77.0 (50.0 - 118.0) |
| **Laboratory tests** | | |
| RBC ($10^{*12}$/L) | 4.5 ± 0.6 | 4.6 (1.8 - 6.6) |
| Hb (g/L) | 139.2 ± 19.6 | 143.0 (58.0 - 187.0) |
| WBC ($10^{*12}$/L) | 5.1 ± 2.1 | 4.7 (1.5 - 22.9) |
| PLT ($10^{*9}$/L) | 129.4 ± 70.6 | 122.0 (25.0 - 552.0) |
| TBIL (umol/L) | 23.7 ± 39.4 | 17.0 (6.4 - 483.3) |
| DBIL (umol/L) | 8.6 ± 26.8 | 4.9 (0.8 - 398.2) |
| IBIL (umol/L) | 14.8 ± 14.9 | 11.9 (0.8 - 221.5) |
| ALB (g/L) | 40.6 ± 5.4 | 40.8 (23.8 - 54.2) |
| ALT (U/L) | 52.1 ± 68.2 | 34.0 (3.0 - 893.0) |
| AST (U/L) | 62.1 ± 109.6 | 37.7 (13.4 - 1560.0) |
| ALP (U/L) | 128.3 ± 102.0 | 107.0 (24.0 - 1743.0) |
| GGT (U/L) | 102.4 ± 119.1 | 62.0 (13.0 - 1079.0) |
| BUN (mmol/L) | 5.5 ± 1.8 | 5.2 (2.2 - 18.4) |
| CR (umol/L) | 72.4 ± 16.1 | 71.8 (36.8 - 166.2) |
| K (mmol/L) | 4.0 ± 0.4 | 4.0 (2.9 - 5.8) |
| Na (mmol/L) | 139.6 ± 2.4 | 139.6 (126.8 - 150.0) |
| Ca (mmol/L) | 2.3 ± 0.1 | 2.3 (1.8 - 3.1) |
| PT (second) | 12.5 ± 1.5 | 12.2 (10.0 - 29.1) |
| APTT (second) | 30.9 ± 5.7 | 29.9 (18.9 - 67.3) |
| INR | 1.1 ± 0.1 | 1.1 (0.9 - 2.5) |
| **Hepatic encephalopathy (No/Grade I-II/Grade III-IV)** | 421/0/0 | |
| **Child-Pugh class (A/B/C)** | 394/27/0 | |
| **Child-Pugh score** | 5.3 ± 0.7 | 5.0 (5.0 - 8.0) |
| **MELD score** | 5.1 ± 3.2 | 4.9 (−2.5 - 25.4) |
| **ALBI grade (1/2/3)** | 240/168/13 | |
| **ALBI score** | −2.6 ± 0.5 | −2.7 (−3.8 - (−0.9)) |
| **MELD-Na score** | −2.2 ± 5.3 | −2.7 (−20.1 - 38.5) |

**Abbreviations**: ALB, albumin; ALBI, albumin-bilirubin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CR, creatinine; DBIL, direct bilirubin; GGT, gamma-glutamyl transpeptidase; IBIL, indirect bilirubin; INR, international normalized ratio; MELD, model for end-stage liver disease; PLT, platelet; PT, prothrombin time; RBC, red blood count; SD, standard deviation; TBIL, total bilirubin; WBC, white blood count.

**Table S3.** Baseline characteristics of patients with ascites.

| Variables | Mean ± SD or Frequency (percentage) | Median (Range) |
|---|---|---|
| Sex (male/female) | 65/9 | |
| Age (years) | 55.2 ± 10.3 | 53.5 (30.0 - 74.0) |
| **Causes of liver diseases, n (%)** | | |
| Hepatitis B virus | 67 (90.5) | |
| Hepatitis C virus | 1 (1.4) | |
| Alcohol | 3 (4.1) | |
| Unknown | 3 (4.1) | |
| **Vital signs** | | |
| Systolic blood pressure (mmHg) | 120.1 ± 15.2 | 116.5 (90.0 - 155.0) |
| Diastolic blood pressure (mmHg) | 75.7 ± 12.8 | 75.0 (50.0 - 105.0) |
| Heart rate (b.p.m.) | 84.0 ± 14.9 | 80.0 (57.0 - 123.0) |
| **Laboratory tests** | | |
| RBC ($10^{*12}$/L) | 3.9 ± 0.9 | 3.9 (1.8 - 6.4) |
| Hb (g/L) | 116.7 ± 26.4 | 120.0 (51.0 - 173.0) |
| WBC ($10^{*12}$/L) | 4.7 ± 2.3 | 4.2 (1.1 - 13.2) |
| PLT ($10^{*9}$/L) | 119.0 ± 101.2 | 89.5 (6.0 - 491.0) |
| TBIL (umol/L) | 49.5 ± 76.2 | 26.2 (4.1 - 419.8) |
| DBIL (umol/L) | 21.0 ± 40.9 | 9.4 (2.0 - 258.7) |
| IBIL (umol/L) | 28.1 ± 44.0 | 17.2 (1.5 - 314.1) |
| ALB (g/L) | 33.8 ± 5.5 | 33.9 (21.7 - 49.9) |
| ALT (U/L) | 71.5 ± 101.8 | 44.1 (12.9 - 699.8) |
| AST (U/L) | 136.9 ± 240.5 | 70.6 (20.2 - 1810.1) |
| ALP (U/L) | 179.6 ± 132.2 | 150.5 (58.0 - 904.0) |
| GGT (U/L) | 192.6 ± 204.5 | 124.0 (7.0 - 906.0) |
| BUN (mmol/L) | 6.1 ± 2.5 | 5.3 (2.4 - 15.9) |
| CR (umol/L) | 69.6 ± 16.4 | 68.6 (35.1 - 127.3) |
| K (mmol/L) | 4.0 ± 0.5 | 4.0 (2.8 - 5.5) |
| Na (mmol/L) | 137.9 ± 4.2 | 138.5 (120.0 - 147.0) |
| Ca (mmol/L) | 2.2 ± 0.1 | 2.2 (1.9 - 2.5) |
| PT (second) | 14.2 ± 2.4 | 13.7 (11.5 - 28.5) |
| APTT (second) | 34.9 ± 9.0 | 32.4 (21.9 - 74.8) |
| INR | 1.2 ± 0.2 | 1.2 (1.0 - 2.2) |
| **Ascites (Mild/Moderate-Severe)** | 51/23 | |
| **Hepatic encephalopathy (No/Grade I-II/Grade III-IV)** | 74/0/0 | |
| **Child-Pugh class (A/B/C)** | 24/42/8 | |
| **Child-Pugh score** | 7.6 ± 1.4 | 7.0 (6.0 - 11.0) |
| **MELD score** | 7.8 ± 4.5 | 7.5 (−3.4 - 21.6) |
| **ALBI grade (1/2/3)** | 9/52/13 | |
| **ALBI score** | −1.9 ± 0.6 | −2.0 (−3.3 - (−0.2)) |
| **MELD-Na score** | 3.1 ± 9.8 | 2.2 (−17.7 - 43.9) |

**Abbreviations**: ALB, albumin; ALBI, albumin-bilirubin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CR, creatinine; DBIL, direct bilirubin; GGT, gamma-glutamyl transpeptidase; IBIL, indirect bilirubin; INR, international normalized ratio; MELD, model for end-stage liver disease; PLT, platelet; PT, prothrombin time; RBC, red blood count; SD, standard deviation; TBIL, total bilirubin; WBC, white blood count.

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# Factors Influencing Patients to Decide to Discharge Themselves against Medical Advice at Tertiary Hospitals: A Cross-Sectional Study

**Malak Alsharif[1], Aeshah Alatawi[2], Abdulhadi M. Alqahtani[3], Mohammed Alufi[4], Faisal Alghamdi[5]**

[1]Emergency Medicine, Ministry of Health, Riyadh, Saudi Arabia
[2]Emergency Medicine, King Fahd Medical City, Riyadh, Saudi Arabia
[3]Clinical Research Department, Research Centre, King Fahd Medical City, Riyadh, Saudi Arabia
[4]Imam Mohammad Ibn Saud Islamic University, Riyadh, Saudi Arabia
[5]Pediatric Emergency, King Fahd Medical City, Riyadh, Saudi Arabia
Email: elsharifbazie@gmail.com

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## Abstract

**Background:** Discharged against medical advice (DAMA) is defined as any instance when a patient wants to leave the hospital against the managing physician's decision. This study aimed to identify factors that influence patients to decide to be DAMA. **Methods:** A descriptive, cross-sectional study. The study was conducted in the emergency department (ED) of King Fahad Medical City (KFMC)-Saudi Arabia-Riyadh city. A questionnaire in both Arabic and English was distributed to all participants to fill in either English or Arabic. **Results:** Between 1 March and 30 April 2021, 510 responses were collected. Most of the study participants (31.4%) were over the age of 54. Our findings showed that 12.5% of our participants had taken discharge against medical advice in the past. **Results Regarding Factors That Influence Patients to Decide on DAMA Showed:** Regarding Inappropriate behavior and disrespect of the physician or staff to the patient and his relatives, 262 (51.4%) participants, 85 (16.7%) participants, and 163 (32%) participants agreed, neutral, and disagreed, respectively. Regarding the Lack of physicians' and nurses' attention to the patient and his relatives (emotionally), our result showed that 278 (54.5%) participants, 95 (18.6%) participants, and 137 (26.9%) participants agreed, neutral, and disagree, respectively. Regarding failure to inform the patient or his relatives of his condition, it showed that 257 (50.4%) participants, 95 (18.6%) participants, and 158 (31%) participants agreed, neutral, and disagreed, respectively. Regarding feeling better from DAMA, our result showed 226 (44.3%) participants, 119 (23.3%) participants, and 165 (32.4%) participants agreed, neutral, and disagreed, respectively. Regarding patients' or their relative's tiredness of hospital stay, the result showed that 166 (32.5%)

participants, 104 (20.4%) participants, and 240 (47.1%) participants agreed, neutral, and disagreed, respectively. **Conclusion:** The long wait time to be seen by a physician was the major factor that forced patients to leave the emergency department against medical advice.

## Keywords

Against Medical Advice, DAMA, Discharge, Factor, Saudi Arabia

## 1. Background

Discharge against medical advice (DAMA) is defined as any instance when a patient wants to leave the hospital against the managing physician's decision [1]. The release may be initiated by the patient, their relatives in an adult patient with competence problems, or by the parents in a child's case. DAMA is a concern for physicians because it disrupts their interactions with the patient and leads to frustration [2]. DAMA has also been associated with adverse health outcomes and increased healthcare costs [3].

Literature review showed patients' reasons for leaving against medical advice include family obligations and financial responsibility. Long waiting times and crowding in the emergency department (ED) are also linked to leaving without being seen by a medical provider, rather than going against medical advice [4].

DAMA is of great concern to many hospital managers and has a wide range of prevalence in the United States. Some studies claim a prevalence of 1% - 2% among general hospital admissions, though in one study from Spain, which included general hospital admissions, the prevalence rate was 0.34% [1] [5].

According to the American College of Emergency Physicians and others, AMA discharges are high-risk situations that can result in malpractice lawsuits. They highly advise that all AMA discharges be carefully documented in the ED chart; every chart should show that the patient knows his or her diagnosis, treatment options, alternative therapies, and the potential repercussions of not following the suggested course of action. Furthermore, the chart should state that no patient should be signed out unless they are deemed competent. After departure from the ED, each patient should receive an equal chance for proper medical follow-up [6].

Predictors of DAMA, such as younger age, male sex, substance abuse, psychological disorders, and a lack of health insurance have been reported in the literature [7]. DAMA exposes the patient to the risk of an insufficiently treated medical problem, which could very easily lead to re-admission and extended morbidity—something that could happen in the next few days to weeks—and it may lead to a longer length of hospital stay for any readmission [6] [8].

Choi *et al.* suggested that DAMA patients be closely monitored via telephone consultations or by a primary physician or nurse's visit to check their condition, preferably within one week of DAMA. Such approaches can potentially have a

big influence on improving patient outcomes, especially in low-income areas. These findings underline the need for more effective healthcare policies that cover the continuum of care after discharge [9].

A study conducted in Saudi Arabia discovered a significant association between age and DAMA. DAMA was more likely to occur among younger patients; this is consistent with the findings of other studies. A study at Princess Nourah Bint Abdulrahman University assessing the demographic factors of DAMA from the ED was the first of its kind conducted in Saudi Arabia [10]. The researchers recommended conducting further studies to investigate the risk factors for DAMA. The present study aimed to determine the most common factors that influence patients to decide on DAMA at a large referral tertiary hospital operated by the Ministry of Health in Riyadh.

## 2. Methods

### 2.1. Study Design/Setting

It is a descriptive, cross-sectional study, and self-administered questionnaire in both Arabic and English. The questionnaire was distributed to all participants to fill in either English or Arabic but not in both.

The study aims to know and study the factors that lead patients to be DAMA.

The study was conducted in the emergency department (ED) of King Fahad Medical City (KFMC). KFMC is a 1200-bed tertiary medical center in Riyadh and one of the largest referral medical centers in Saudi Arabia. Study duration from 1st March to 30 April 2021.

### 2.2. Inclusion and Exclusion Criteria

***Inclusion criteria*:**

1) All patients who attended our ED during the study period.
2) Patient who was 18 years old and above.
3) Patients who were mentally healthy.

***Exclusion criteria*:**

1) Patients less than 18 years old.
2) Patients with abnormal mental health status.
3) Patients who had acute psychosis were intoxicated and critically ill.
4) Incomplete data.

### 2.3. Questionnaire Development

Previous studies were reviewed to determine the most common factors influencing patients to decide on DAMA [9]. Our questionnaire was modified to fit the study's aim. The questionnaire consisted of 21 questions that were classified into two main sections. The first section consisted of sociodemographic characteristics, such as age, gender, marital status, residential area, number of children (if any), educational level and background, where the patient typically seeks medical treatment, and level of health insurance (if any). The second section eva-

luated the factors that influence patients to decide on DAMA.

A pilot study was carried out among ten patients at KFMC to ensure good reliability; Cronbach's alpha was 0.735, indicating the good reliability of our tool, and no substantive changes were made to the questionnaire after the pilot study. The factors' influence domain was assessed using a Likert scale (agree, neutral, and disagree).

### 2.4. Data Collection

Four volunteers had access to the hospital questionnaire for patients who wanted to discharge themselves or their relative against medical advice and collected the data; all the volunteers had a medical background (e.g., they were students or graduate students in medical sciences). The questionnaire was administered electronically using Google Forms.

### 2.5. Sample Size

The sample size was calculated using Raosoft sample size calculator soft word [11]. We used the universally acceptable confidence interval (CI) of 95%, with a standard deviation (SD) of 0.5 and a margin of error of 5%.

### 2.6. Statistical Analysis

Data analysis was performed using SPSS 25.0 software (SPSS Inc., Chicago, IL, USA). We used a descriptive-frequency test and the Chi-square test to determine the intensity of the correlation among independent variables (age, gender, educational level, and marital status) and the factors that influence patients.

## 3. Result

The study was conducted from 1 March to 30 April 2021 at KFMC-Riyadh-Saudi Arabi. The total number of patients who participated in the study was 510 patients.

Gender distribution showed males were 267 (52.4%) and females were 243 (47.6%).

In our study population, those between 18 to 30 years old were 120 (23.5%) patients, 31 to 42 years old were 107 (21.0%) patients, 43 to 54 years old were 123 (24.1%) patients, and more than 54 years old were 160 (31.4) patients, **Table 1**.

Regarding marital status, 352 patients were married. Saudi patients were 4829 (94.5%) patients, and 28 (5.5%) patients were non-Saudi, 371 (72.7%) patients currently resided in Riyadh city.

Our population study showed those with children were 324 (92.04%) patients, and those who had no children were 28 patients (7.95%) patients.

The educational level of our study population showed that uneducated (illiterate) was 70 (13.7%) patients, Elementary school level 32 (6.3%) patients, Middle/High School level 192 (37.6%) patients, and Bachelor's degree 184 (36.1%)

patients, Master's degree 24 (4.7%) patients, and Ph.D. degree in eight (1.6%) patients.

The study showed that 389 (76.3%) patients took their treatment in a governmental hospital, and 121 (23.7%) patients were treated in a private hospital.

A participant with Medical Health insurance was 126 (24.7%) patients and 384 (75.3%) patients without medical health insurance.

**Results regarding factors that influence patients to decide on DAMA showed: Table 2 [n = 512]**

Regarding Inappropriate behavior and disrespect of the physician or staff to the patient and his relatives, 262 (51.4%) participants, 85 (16.7%) participants, and 163 (32%) participants agreed, neutral, and disagreed, respectively.

**Table 1.** Demographic information (n = 510).

| | | n | % |
|---|---|---|---|
| **Age** | 18 - 30 y | 120 | 23.5 |
| | 31 - 42 y | 107 | 21.0 |
| | 43 - 54 | 123 | 24.1 |
| | >54 y | 160 | 31.4 |
| **Gender** | Male | 267 | 52.4 |
| | Female | 243 | 47.6 |
| **Marital status** | Single | 158 | 31.0 |
| | Married | 352 | 69.0 |
| **Nationality** | Saudi | 482 | 94.5 |
| | Non-Saudi | 28 | 5.5 |
| **(If the answer is married), Do you have children** | Yes | 324 | 92.04 |
| | No | 28 | 7.95 |
| **Where is your current residence?** | Riyadh | 371 | 72.7 |
| | Outside Riyadh | 139 | 27.3 |
| **Educational level** | Uneducated | 70 | 13.7 |
| | Elementary school | 32 | 6.3 |
| | Middle /high school | 192 | 37.6 |
| | Bachelor's degree | 184 | 36.1 |
| | Master's degree | 24 | 4.7 |
| | PhD's degree | 8 | 1.6 |
| **Where do you always take your treatment?** | Government hospitals | 389 | 76.3 |
| | Private hospitals | 121 | 23.7 |
| **Do you have medical insurance?** | Yes | 126 | 24.7 |
| | No | 384 | 75.3 |
| **Have you ever discharged against medical advice?** | Yes | 64 | 12.5 |
| | No | 446 | 87.5 |

**Table 2.** Factors influence patients to decide of discharge against medical advice (n = 510).

| | Agree | | Neutral | | Disagree | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| **Inappropriate behavior and disrespect of the physician or staff to the patient and his relatives** | 262 | 51.4 | 85 | 16.7 | 163 | 32.0 |
| **Lack of physicians and nurses' attention to the patient and his relatives (emotionally)** | 278 | 54.5 | 95 | 18.6 | 137 | 26.9 |
| **Failure to inform the patient or his relatives of his condition** | 257 | 50.4 | 95 | 18.6 | 158 | 31.0 |
| **Feeling better** | 226 | 44.3 | 119 | 23.3 | 165 | 32.4 |
| **Patients or their relative's tiredness of hospital stay** | 166 | 32.5 | 104 | 20.4 | 240 | 47.1 |
| **Having relatives in home for which patient is personally responsible** | 226 | 44.3 | 87 | 17.1 | 197 | 38.6 |
| **Having familial or social issues** | 122 | 23.9 | 76 | 14.9 | 312 | 61.2 |
| **Looking for other medical opinion** | 226 | 44.3 | 123 | 24.1 | 161 | 31.6 |
| **Unexpected management plan** | 187 | 36.7 | 139 | 27.3 | 184 | 36.1 |
| **financial issues: (Accommodation, transportation)** | 168 | 32.9 | 102 | 20.0 | 240 | 47.1 |
| **Long waiting time to be seen by physician** | 291 | 57.1 | 65 | 12.7 | 154 | 30.2 |
| **Lack of admission beds in relevant wards** | 265 | 52.0 | 86 | 16.9 | 159 | 31.2 |

Regarding the lack of physicians' and nurses' attention to the patient and his relatives (emotionally), our result showed that 278 (54.5%) participants, 95 (18.6%) participants, and 137 (26.9%) participants agreed, neutral, and disagree, respectively.

Regarding failure to inform the patient or his relatives of his condition, it showed that 257 (50.4%) participants, 95 (18.6%) participants, and 158 (31%) participants agreed, neutral, and disagreed, respectively.

Regarding feeling better from DAMA, our result showed 226 (44.3%) participants, 119 (23.3%) participants, and 165 (32.4%) participants agreed, neutral, and disagreed, respectively.

Regarding patients' or their relative's tiredness of hospital stay, the result showed that 166 (32.5%) participants, 104 (20.4%) participants, and 240 (47.1%) participants agreed, neutral, and disagreed, respectively.

Regarding having relatives in the home for which the patient is personally responsible, the result showed that 226 (44.3% ) participants, 87 (17.1%) participants, and 197 (38.6%) participants agreed, neutral, and disagreed, respectively.

Regarding having familial or social issues, the result showed that 122 (23.9%) participants, 76 (14.9%) participants, and 312 (61.2%) participants agreed, neutral, and disagreed, respectively.

Regarding looking for another medical opinion, the result showed that 226 (44.3%) participants, 123 (24.1%) participants, and 161 (31.6%) participants agreed, neutral, and disagreed, respectively.

Regarding the unexpected management plan, the result showed that 187 (36.7%) participants, 139 (27.3%) participants, and 184 (36.1%) participants

agreed, neutral, and disagreed, respectively.

Regarding financial issues: (Accommodation, transportation) as a cause to decide DAMA, it showed that 168 (32.9%) participants, 102 (20%) participants, and 240 (47.1%) participants agreed, neutral, and disagreed, respectively.

Regarding the long waiting time to be seen by a physician as a cause to decide on DAMA, it showed that 291 (57.1%) participants, 65 (12.7%) participants, and 154 (30.2%) participants were agreed, neutral, and disagree respectively.

Regarding the lack of admission beds in relevant wards as a cause to decide DAMA it showed that 265 (52%) participants, 86 (16.9%) participants, and 159 (31.2%) participants agreed, neutral, and disagreed, respectively.

Our findings indicate that, by far, the primary reason patients decide on DAMA is the long waiting time before being seen by a physician ($P \geq 0.001$). We also found a significant association between the decision to choose DAMA and the idea of inappropriate behavior or disrespect by the physician and other staff toward the patient and their relatives ($P = 0.024$). We also found a significant association between DAMA and the Failure to inform the patient or their relatives about the patient's condition ($P = 0.032$). Other significant correlating reasons for choosing DAMA were feelings of tiredness among the patient or their relatives and the presentation of an unexpected management plan ($P = 0.010$ and 0.030, respectively; Table 3).

Table 3. Association between patients discharged against medical advice and factor influencing patients (n = 510).

| | | Have you ever discharged against medical advice? | | |
|---|---|---|---|---|
| | | **Yes** | **No** | P-value |
| **Age** | 18 - 30 y | 11 | 109 | 0.066 |
| | 31 - 42 y | 9 | 98 | |
| | 43 - 54 y | 23 | 100 | |
| | >54 y | 21 | 139 | |
| **Gender** | Male | 40 | 227 | 0.082 |
| | Female | 24 | 219 | |
| **Marital status** | Single | 12 | 146 | 0.024* |
| | Married | 52 | 300 | |
| **Educational level** | Uneducated | 9 | 61 | 0.861 |
| | Elementary school | 4 | 28 | |
| | Middle/high school | 22 | 170 | |
| | Bachelor's degree | 25 | 159 | |
| | Master's degree | 4 | 20 | |
| | Ph.D.'s degree | 0 | 8 | |
| **Inappropriate behavior and disrespect of the physician or staff to the patient and his relatives** | Agree | 39 | 223 | 0.024* |
| | Neutral | 14 | 71 | |
| | Disagree | 11 | 152 | |

Continued

| | | | | |
|---|---|---|---|---|
| **Lack of physicians and nurses' attention to the patient and his relatives (emotionally)** | Agree | 41 | 237 | 0.092 |
| | Neutral | 13 | 82 | |
| | Disagree | 10 | 127 | |
| **Failure to inform the patient or his relatives of his condition** | Agree | 42 | 215 | 0.032* |
| | Neutral | 9 | 86 | |
| | Disagree | 13 | 145 | |
| **Feeling better** | Agree | 31 | 195 | 0.743 |
| | Neutral | 13 | 106 | |
| | Disagree | 20 | 145 | |
| **Patients or their relative's tiredness of hospital stay** | Agree | 29 | 137 | 0.010* |
| | Neutral | 16 | 88 | |
| | Disagree | 19 | 221 | |
| **Having relatives in a home for which the patient is personally responsible** | Agree | 26 | 200 | 0.093 |
| | Neutral | 17 | 70 | |
| | Disagree | 21 | 176 | |
| **Looking for another medical opinion** | Agree | 28 | 198 | 0.985 |
| | Neutral | 16 | 107 | |
| | Disagree | 20 | 141 | |
| **Unexpected management plan** | Agree | 33 | 154 | 0.030* |
| | Neutral | 14 | 125 | |
| | Disagree | 17 | 167 | |
| **financial issues: (Accommodation, transportation)** | Agree | 20 | 148 | 0.880 |
| | Neutral | 12 | 90 | |
| | Disagree | 32 | 208 | |
| **Long waiting time to be seen by a physician** | Agree | 51 | 240 | <0.001* |
| | Neutral | 3 | 62 | |
| | Disagree | 10 | 144 | |
| **Lack of admission beds in relevant wards** | Agree | 37 | 228 | 0.360 |
| | Neutral | 12 | 74 | |
| | Disagree | 15 | 144 | |

*The significant P-value.

## 4. Discussion

DAMA remains a significant healthcare problem, constituting a major adverse effect on healthcare systems and patient care. DAMA exposes patients to the risk of untreated medical issues, an increased readmission rate, and an extended recovery period and morbidity [6].

Some studies have shown that DAMA is a significant strain on healthcare sys-

tems and a direct cause of wasted resources. Over five years, incurred costs due to DAMA are estimated to be nearly $3 billion [12]. The calculated costs due to DAMA are 56% higher than those expected from a patient's initial hospitalization [1]. This increase in cost could be secondary to several reasons, such as a more extended readmission period, double care by physicians and nurses, and extra work-ups on the patient due to care needed to treat complications that may have occurred.

Only 12.5% of our participants reported having ever signed a DAMA; it was near the average of 13.2%, derived from three studies published in Iran [13] [14] [15].

In our study, we found that educational level has no impact on a patient's decision to sign DAMA. We found most of our participants who signed a DAMA were over the age of 43, which is in contrast to a study conducted in Pakistan [16] [17].

Our findings indicate that gender is not a major factor influencing patients' decisions related to DAMA, unlike other studies showing a significant male predominance [13] [17] [18]. Marital status was associated with DAMA (P = 0.024), which is compatible with the study conducted in Iran [13].

We found that the significant factor that would influence our patients to choose DAMA was the long time spent waiting to be seen by a physician, with a P-value of 0.001, followed by the tiredness related to the hospital stay (P = 0.010). Followed by inappropriate behavior and disrespect by staff (P = 0.024), an unexpected management plan, and a failure to inform the patient or their relatives about their condition came next, with P-values of 0.030 and 0.032, respectively. These findings correlate well with findings from other studies [19] [20].

Concerns about the lack of available beds in relevant wards were not significant in our study (P = 0.360), which could be due to the availability of private rooms and suitable accommodation in the ER and the same standard of care provided there as in the wards.

Regarding factors like physicians' and nurses' attention to the patient and their relatives' emotional support, financial issues, looking for another medical opinion, having relatives at home for which the patient is personally responsible, feeling better, and educational level, we noted only insignificant correlations with DAMA decisions. Other studies showed that financial concerns and insurance had a significant effect [8] [18] [19].

### Limitations

The study was conducted at one site, which may not reflect the true range of impressions and opinions of all citizens of Saudi Arabia.

## 5. Conclusions

A long wait time before being seen by a physician, inappropriate behavior, and staff disrespect were the significant factors that prompted patients to discharge

themselves from a hospital against medical advice respectively.

The educational level of participants and the need for more available beds have no impact on the decision to sign DAMA.

## Recommendations

Our recommendation for future study is to conduct qualitative interviews with patients and healthcare providers to explore in greater depth the factors that lead to DAMA actions and develop proper solutions to reduce and avoid DAMA decisions. The implementation of a new form or method for use at Saudi hospitals to capture all the reasons for DAMA at a national level would also facilitate studies of the phenomenon in the future.

We also recommend mandatory communication skills courses for all physicians during their training. Future studies should also assess emergency doctors' opinions regarding DAMA actions.

## Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki. Permission to conduct this study was obtained from the institutional review board at KFMC (project No. 21-105). Electronic informed consent was provided by each participant before they answered the questionnaire. Participants received no compensation for their participation in the study.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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## Abbreviations

DAMA: Discharge against Medical Advice.
ED: Emergency Department.
AMA: Against Medical Advice.
KFMC: King Fahad Medical City.
CI: Confidence Interval.
SD: Standard Deviation.
SPSS: Statistical Package for the Social Sciences.

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# Rifaximin in the Treatment of Gastroesophageal Reflux Disease: A New Idea Based on the Relationship between Intestinal Microecology and Gastroesophageal Reflux Disease

**Di Yang[1*], Guangyang Zheng[1], Peilong Wang[2*], Lei Huang[2]**

[1]The First Clinical College, Changzhi Medical College, Changzhi, China
[2]Department of Endoscopy, Heji Hospital, Changzhi Medical College, Changzhi, China
Email: *1414538422@qq.com, *peilongwang06@163.com

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## Abstract

Gastroesophageal Reflux Disease (GERD) is a common clinical disorder, the most common symptom of which is a burning sensation behind the breastbone (heartburn) or reflux of stomach contents into the upper pharynx (acid reflux). The prevalence in China is increasing year by year, which can affect the quality of life of patients and also increase the economic burden on families and society. The pathogenesis of GERD is still unclear, and some studies suggest that intestinal microecology may be closely related to the development of GERD. Rifaximin is not readily absorbed orally and acts locally in the intestine, so it has mild adverse effects and good safety, and can be used to treat gastrointestinal diseases such as irritable bowel syndrome, traveler's diarrhea, small intestinal bacterial overgrowth, diverticulosis, inflammatory bowel disease and hepatic encephalopathy. Therefore, this paper focuses on intestinal microecology as a possible pathogenesis of GERD and further explores the feasibility of rifaximin for the treatment of GERD.

## Keywords

Gastroesophageal Reflux Disease, Intestinal Microecology, Rifaximin

## 1. Introduction

Gastroesophageal reflux is a common clinical condition, and it is estimated that about 20% of the adult population in the Western world suffers from GERD [1],

and the prevalence in China is increasing year by year, and population-based epidemiological surveys in China have shown that the prevalence of at least one episode of heartburn symptoms per week is 1.9% to 7.0% [2] [3]. The most common symptom of GERD is a burning sensation behind the sternum (heartburn) or reflux of gastric contents into the upper throat (acid reflux), and recurrent episodes of GERD can affect the quality of life of patients and also increase the economic burden on families and society. The mechanism of GERD is still unclear and its pathogenesis is multifactorial, such as: anti-reflux barriers, esophageal clearance and weakened esophageal mucosal resistance [4], and several recent studies have shown that small intestinal bacterial overgrowth is significantly higher in populations where GERD occurs than in normal populations, and Jordan J. Haworth *et al.* [5] showed for the first time that refractory GERD symptoms may be the result of altered gut microbiota result. Currently proton pump inhibitors (PPIs: proton pump inhibitors) are still the drug of choice for the treatment of GERD to induce remission and maintenance therapy; however, some articles have reported that long-term PPI intake is likely to cause several complications such as: osteoporosis, fractures, micronutrient deficiencies, chronic kidney disease, and can even increase the risk of novel coronavirus pneumonia infection, etc. [6] [7] [8] [9], where long-term PPI use may also lead to changes in the structure of the intestinal flora. Therefore, it seems to be contradictory that the alteration of intestinal microecology caused by PPIs in the treatment of GERD may also cause the occurrence of GERD. In this paper, we focus on the feasibility of rifaximin treatment for GERD, starting from the fact that intestinal microecology may be the pathogenesis of GERD.

## 2. Definition and Diagnosis of GERD

GERD is a multifaceted disease that includes a series of syndromes caused by or exacerbated by gastroesophageal reflux. These syndromes mainly cause morbidity through troublesome symptoms, of which heartburn and reflux are typical symptoms of GERD, and some of them only show atypical symptoms and extra-esophageal symptoms. According to the Montreal definition, "GERD is a disease with uncomfortable symptoms and/or complications caused by the reflux of gastric contents." The strength of this definition lies in its simplicity, combining a number of symptoms with potential complications. While the Lyon consensus remains positive about diagnosing GERD by typical symptoms and by empirical PPI treatment, the Lyon consensus focuses more on making a diagnosis of GERD in physiological morphology, by evaluating various diagnostic tests including upper gastrointestinal endoscopy, 24-hour dynamic pH or pH-impedance monitoring, esophageal high-resolution manometry, and by providing various definitive diagnostic and exclusionary parameters to give specific definitions [10].

## 3. Pathogenesis of GERD

Although GERD is a common clinical disease, its pathogenesis is quite complex,

involving the interaction of chemical, mechanical, psychological and neurological mechanisms. Under normal conditions, intra-abdominal pressure is positive while intrathoracic pressure is negative, a physical principle that should promote reflux of gastric contents into the esophagus. Not surprisingly, small amounts of reflux occur in everyone throughout the day, but pathological GERD is prevented by the normal anatomy and physiology of the esophagus, the lower esophageal sphincter (LES), the transverse septum at the foramen ovale, and the stomach. In general, the LES is the most important physiological structure of the normal reflux barrier [11] [12], but it may also be due to increased pressure gradients between the abdomen and the chest (e.g. morbid obesity and pregnancy) or impaired motility of the esophagus, the muscles of the foramen ovale and/or the stomach. Some recent studies suggest that alterations in intestinal microecology likewise play an important role in the development of GERD.

## 4. Relationship between GERD and Intestinal Microecology

### 4.1. Small Intestinal Bacterial Overgrowth and GERD

Based on the gross endoscopic presentation of the esophageal mucosa, GERD is divided into three types, namely Barrett's esophagus (Barrett's esophagus), reflux esophagitis (RE), and non-erosive gastroesophageal reflux disease (non -In 2012, a pilot study was conducted by Kim *et al.* [13] who hypothesized a possible relationship between RE and small intestinal bacterial overgrowth (SIBO) may have a relationship with each other. Since bacteria are the only source of intestinal hydrogen and methane, hydrogen and methane gas in the exhaled breath were used as markers of colonic fermentation, and they compared the prevalence of SIBO in healthy subjects and RE subjects separately by the lactulose hydrogen breath testing (LHBT). The results showed that 19 of 28 RE patients had abnormal LHBT (67%) compared to 11 of 29 controls (37%) and that the prevalence of SIBO was higher in RE subjects than in controls, an association that was statistically significant. Their preliminary data support this new hypothesis that SIBO may be an important prevalence factor in some GERD patients.

### 4.2. Colonic Fermentation and GERD

In 2021 Tanisa Patcharatrakul *et al.* [14] conducted a randomized crossover study of 21 patients with GERD to assess the effect of the level of low short-chain carbohydrates (FODMAPs) in food on typical GERD symptoms and the correlation between GERD symptoms and intestinal gas production. The results showed that after ingestion of wheat flour with high FODMAPs, patients experienced increased bloating, satiety and chest discomfort, maximum reflux symptoms after 15 minutes compared to rice with low FODMAPs, and reflux severity scores were significantly and positively correlated with the area under the curve of exhaled hydrogen concentration and the area under the curve of methane concentration. This study showed that wheat flour with high levels of FODMAPs was more likely to produce typical GERD symptom scores after a meal, especially 15

minutes after lunch, and that the effect of wheat pasta on GERD symptoms was associated with increased gut gas production after lunch, confirming a link between GERD symptoms and colonic fermentation.

Most carbohydrates are metabolized by colonic bacterial flora to short-chain fatty acids (SCFA) and hydrogen gas, and A Ropert *et al.* [15] found that gastric tone was also reduced by intracolonic infusion of lactose and short-chain fatty acids, with the most pronounced effect after the highest dose of SCFA; similarly, Suppawatsa Plaidum *et al.* [16] assessed immediately after lunch for 2 hours after TLESR and monitored for 2 hours, during the first 30 minutes of recording (1.38 ± 0.32 versus 0.50 ± 0.19 beats/30 minutes, $p < 0.05$), 30 - 60 minutes (1.38 ± 0.32 versus 0.75 ± 0.16 beats/30 minutes, $p < 0.05$) and 60 - 90 minutes after the meal (1.63 ± 0.38 versus 0.63 ± 0.18 beats/30min, $p < 0.05$), it was found that the intake of wheat flour significantly produced more TLESR events than the intake of rice flour in the 2 hours after lunch. It was also found that wheat ingestion was significantly associated with higher hydrogen and methane levels after lunch compared to rice ingestion, and that the area under the hydrogen and methane concentration curve was significantly associated with the number of TLESR events. Their findings suggest that FODMAPs meals may regulate TLESR through colonic fermentation or intestinal $H_2$ production.

Thus, disturbances in intestinal microecology may contribute to the development of GERD: 1) small intestinal bacterial overgrowth can lead to fermentation of food in the intestine, and excessive gas production can increase the pressure gradient between the abdomen and the chest, contributing to the development of reflux; 2) fermentation in the intestine decreases the LES pressure, causing a significant increase in the occurrence of postprandial TLESR; 3) excessive fermentation products can reduce gastric tone, leading to prolonged gastric emptying time and an increased chance of reflux occurrence.

## 5. Treatment of GERD—PPI Use and Disturbance of Intestinal Microecology

Four different modalities are currently available for the treatment of GERD: 1) lifestyle modification, 2) pharmacological treatment, 3) endoscopic intervention, and 4) surgery.

In terms of lifestyle, patients can be asked to elevate the head of the bed and avoid late night meals, advised to avoid alcohol, smoking, and foods such as chocolate, coffee, and carbonated beverages, and, most importantly, to lose weight [17]. Currently, the American Gastroenterological Association states in its recent guidelines that current endoscopic treatment should not be considered as an alternative to pharmacological or surgical treatment [18] and that treatment options remain between PPI and surgery. However, for the choice between medical medication and surgical treatment, patients tend to prefer endoscopic treatment first and opt for surgical treatment only after ineffective medical treatment and rigorous evaluation.

In terms of medical treatment, histamine receptor antagonists and PPIs have been the main agents of treatment, and studies of the new acid-suppressing drug potassium channel acid blocker (P-CAB) in the treatment of RE patients have shown a mucosal healing rate of about 90% at 4 weeks after treatment, and its representative drug, vornoprazine, also has a slightly higher healing rate than the lansoprazole group [19]. Therefore, PPI or P-CAB is the drug of choice for the treatment of GERD, this is because it is more effective than histamine receptor antagonists in relieving symptoms and curing esophagitis, and the recommended course of treatment for GERD with PPI or P-CAB is 4 - 8 weeks.

### 5.1. PPI and Intestinal Flora

PPIs are widely used and readily available in clinical settings, and are commonly used by clinicians to prevent the development of stress ulcers or to reduce gastrointestinal toxicity associated with certain medications, and proton pump inhibitors are often overused in outpatient care settings without a documented effective indication [20]. However, it is worth noting that long-term use of PPIs is by no means risk-free, and possible associations have been reported for osteoporosis, fractures, and micronutrient deficiencies [6] [7] [8] [9], and numerous studies have shown that PPI use is closely associated with C. difficile infection and recurrence, and recent meta-analyses have confirmed this view [21].

Human intestinal bacteria have a large population with genes about 100 times larger than the genome [22], and thanks to the remarkable development of gene sequencing, we can now determine bacterial species and their numbers faster and more economically compared to the past, and it has been confirmed that the long-term use of PPIs can lead to significant changes in the diversity and composition of the intestinal microbiota. In 2015, Matthew A Jackson *et al.* [23] investigated the association between PPI use and gut microbiota by 16S ribosomal RNA amplification from stool samples of 1827 healthy twins, and PPI users had significantly lower abundance of gut commensal bacteria, lower microbial diversity, and associated significantly increased abundance of oral and upper gastrointestinal commensal bacteria. Gastric acid is important in the digestion and absorption of food and medications and in maintaining a relatively sterile gastric environment, and many pathogens cannot survive in a highly acidic environment, so a decrease in gastric acid production may increase the risk of infection transmission through fecal-oral contact. What we can assume is that under normal conditions, gastric acid is a barrier to the downward movement of pharyngeal commensal and environmental bacteria along the gastrointestinal tract and that these bacteria do not adapt well to low pH. Treatment with PPI removes this barrier and allows further colonization of these bacteria along the gastrointestinal tract, and these bacteria can reach more distal parts of the gastrointestinal tract, with the resulting changes in the gut microbiota, as shown in a meta-analysis by Wai-Kit Lo *et al.* [24] in 2013, in a study using duodenal or jejunal aspirate cultures for the diagnosis of SIBO, where SIBO was associated with PPI use, but no relationship was found between SIBO and PPI use in studies using

glucose hydrogen breath tests, which explains the different previous findings that may be associated with poor diagnostic accuracy.

### 5.2. Regulation of Intestinal Flora Improves GERD

Moreover, PPI treatment for GERD still leaves some patients with insignificant symptom relief or rapid re-emergence of symptoms after discontinuation of the drug. 2020 Chinese GERD Guidelines and Consensus consider that those with no significant improvement in symptoms such as reflux and heartburn after double standard dose and 8-week course of acid suppressant treatment are defined as refractory GERD, and those with symptoms that are not controlled after adequate acid suppressant treatment and the presence of Anti-reflux surgery may be considered if symptoms are associated with reflux [25]. 2020 Jordan J. Haworth *et al.* [5] retrospectively evaluated data from patients referred to specialized reflux centers (n = 104) and found a high prevalence of gut flora dysbiosis in GERD patients and a seemingly increased likelihood of positive reflux symptoms, a common indication for anti-reflux surgery. These patients were more likely to report gas-related symptoms prior to anti-reflux surgery, and therefore endogenous bacterial fermentation in the small intestine is presumed to be a contributing factor to refractory reflux symptoms.

In 2021, Zheng, Y. M. *et al.* [26] suggested that recurrence of symptoms and long-term PPI use in patients with GERD (including NERD) may be related to changes induced by gut microbiota and SIBO after previous PPI use, and they investigated whether washed microbiota transplantation (WMT: washed microbiota transplantation) to see if it improves the symptoms of proton pump inhibitor-dependent non-celiac reflux disease. The total remission rate in the WMT and PPI groups was 93.3% vs 41.7%. Compared with the PPI group, the WMT group showed better results in the GERDQ scores (7 vs 11, $p = 0.004$) and RDQ scores (8 vs 20.5, $p = 0.003$), as well as in the remission months [8 (3, 17) vs 2 (0, 4), $p = 0.002$]. Compared with the PPI group, the WMT group showed better results in terms of GERDQ score and RDQ score as well as months of remission, which were statistically significant. WMT significantly relieved the symptoms of NERD patients, reduced PPI dependence, prolonged symptom remission, reduced relapse, and also increased the diversity and balance of the bacterial community.

During treatment with proton pump inhibitors, changes in the intestinal microbiota, such as reduced microbial diversity or small intestinal bacterial overgrowth, can result from the alteration of the acid-base environment in the intestine where bacteria live, yet the altered intestinal microecology may also contribute to the development of GERD, and therefore there are conflicting aspects of treatment with PPIs.

## 6. Rifaximin—A Broad-Spectrum Antibiotic for the Intestine

Rifaximin, a semi-synthetic derivative of rifamycin SV, is a broad-spectrum intestinal antibiotic. The in vitro antibacterial activity of rifaximin shows that it

has high antibacterial activity against Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus and Clostridium difficile among the Gram-positive aerobic bacteria, and rifaximin is almost not absorbed after oral administration (absorption < 1%), and only acts locally in the gastrointestinal tract, so it has a very high concentration in the intestinal tract and is rarely distributed in other organs, and it has a wide antibacterial spectrum, so it is a kind of drug used for local intestinal infections and is mostly used for the treatment of travelers' diarrhea, hepatic encephalopathy and irritable bowel syndrome [27].

Animal studies suggest that the use of antibiotics such as vancomycin, imipenem and ciprofloxacin can greatly reduce the diversity in the intestinal microbiota and increase antibiotic resistance [28]. However, rifaximin maintains and functionally regulates the overall composition and diversity of the intestinal microbiota and may reduce the abundance of harmful bacteria (e.g., Klebsiella, Streptococcus, and Clostridium) and increase the abundance of probiotic bacteria (e.g., Bifidobacterium and Synechococcus) [29]. Hiccups and bloating are common symptoms in patients with GERD, and in a randomized, double-blind, placebo-controlled trial, patients with bloating responded positively to rifaximin and symptom improvement was associated with a reduction in $H_2$ expiratory excretion [30], and Tan *et al.* [31] found that rifaximin relieved hiccups and postprandial bloating in patients with functional dyspepsia without IBS. Given the properties of rifaximin, which may reset the microbial diversity in the environment and reduce bacterial fermentation, thus reducing the occurrence of GERD, and presumably reducing the occurrence of intestinal microecological disorders due to long-term PPI use and reducing the recurrence of GERD after PPI discontinuation.

## 7. Conclusion and Outlook

The intestinal microecology is a huge microbiota in the human body, and its composition is also complex. Changes in the intestinal microecology can lead to a series of pathologies in the body, and is far from being limited to the digestive tract. Thanks to a number of studies at home and abroad, we initially found that the intestinal flora and the occurrence of GERD may be inextricably linked, as long-term PPI treatment of GERD often leads to the dysbiosis of the intestinal flora, which may contribute to the occurrence of GERD in the process of treatment. However, the mechanism of intestinal microecological disorders causing reflux is still unclear and needs to be discovered and verified by deeper studies, and there is also a lack of prospective studies pointing to the effectiveness of rifaximin in the treatment of GERD. Therefore, it is expected that more studies will be conducted in the near future to reveal the relationship between intestinal microecology and GERD and to enrich the therapeutic diversity.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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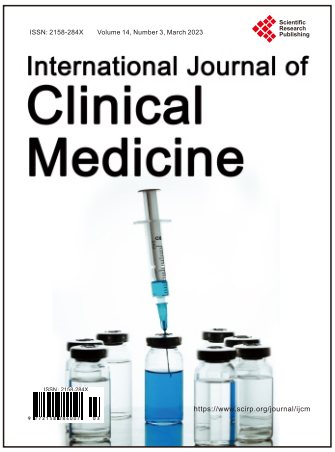


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- Clinical Neurology and Neurosurgery
- Clinical Neurophysiology
- Clinical Neuropsychology
- Clinical Neuroradiology
- Clinical Neuroscience
- Clinical Nursing
- Clinical Nutrition
- Clinical Obstetrics and Gynaecology
- Clinical Oncology and Cancer Research
- Clinical Ophthalmology
- Clinical Oral Implants Research
- Clinical Oral Investigations
- Clinical Orthopaedics and Related Research
- Clinical Otolaryngology
- Clinical Pathology
- Clinical Pediatric Emergency Medicine
- Clinical Periodontology
- Clinical Pharmacology & Toxicology
- Clinical Pharmacy and Therapeutics
- Clinical Physiology and Functional Imaging
- Clinical Practice and Epidemiology in Mental Health
- Clinical Psychology and Psychotherapy
- Clinical Psychology in Medical Settings
- Clinical Radiology
- Clinical Rehabilitation
- Clinical Research and Regulatory Affairs
- Clinical Research in Cardiology
- Clinical Respiratory
- Clinical Rheumatology
- Clinical Simulation in Nursing
- Clinical Sleep Medicine
- Clinical Techniques in Small Animal Practice
- Clinical Therapeutics
- Clinical Toxicology
- Clinical Transplantation
- Clinical Trials
- Clinical Ultrasound
- Clinical Virology
- Complementary Therapies in Clinical Practice
- Consulting and Clinical Psychology
- Contemporary Clinical Trials
- Controlled Clinical Trials
- Diabetes Research and Clinical Practice
- Evaluation in Clinical Practice
- Fundamental & Clinical Pharmacology
- Hereditary Cancer in Clinical Practice
- Human Psychopharmacology: Clinical and Experimental
- Innovations in Clinical Neuroscience
- Laboratory and Clinical Medicine
- Neurophysiologie Clinique/Clinical Neurophysiology
- Nutrition in Clinical Practice
- Pacing and Clinical Electrophysiology
- Psychiatry in Clinical Practice
- Therapeutics and Clinical Risk Management
- Veterinary Clinical Pathology

We are also interested in short papers (letters) that clearly address a specific problem, and short survey or position papers that sketch the results or problems on a specific topic. Authors of selected short papers would be invited to write a regular paper on the same topic for future issues of the ***IJCM***.

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