Efficacy of Ursodeoxycholic Acid in Nonalcoholic Fatty Liver Disease: An Updated Meta-Analysis of Randomized Controlled Trials

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Abstract

Background

Nonalcoholic fatty liver disease (NAFLD) is a kind of chronic liver disease among general population. Recent years, more and more new experiments have made the role of ursodeoxycholic acid (UDCA) become clearer. In this meta-analysis, we analyzed the efficacy of ursodeoxycholic acid (UDCA) for the treatment of nonalcoholic fatty liver disease (NAFLD).

Methods

We searched the Web of Science, Pubmed, Embase and Cochrane library databases for relavent studies published before March 1, 2019. We examined 134 randomized controlled trials (RCTs) that investigated the effectiveness of UDCA in NAFLD against placebo or other treatments. Next, we conducted meta-analysis by Stata(version 12.0) to examine the change among several indices: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), Alkaline phosphatase (AP), total bilirubin and albumin.

Results

Following the application of different inclusion and exclusion criteria, 9 articles with 1106 participants were finally selected. The forest plot displayed that UDCA treatment can significantly decrease the ALT levels among the NAFLD patients (SMD=0.17,95%CI [0.03 to 0.3], P=0.07). However, UDCA treatment did not significantly affect the AST, GGT, AP, total bilirubin and albumin levels. Further, the subgroup analyses suggested the significant role of UDCA treatment in different geographical regions, age group and treatment duration (P=0.003 in people from Europe, P=0.001 in people older than 50 years and P=0.008 in longer duration(>6 months)).

Conclusion

In this study, several indices we analyzed among 9 articles. UDCA treatment was found beneficial in lowering the ALT levels in NAFLD patients. The remaining indices like AST, GGT, AP showed non-significant changes in this analysis. This could be attributed for the insufficient number of trials because all parameters were not analyzed in each individual RCT. Therefore, future meta-analysis will be required to fully confirm and validate the efficacy of UDCA in NAFL.

Introduction

Along with the increased incidence of obesity and other metabolic diseases, nonalcoholic fatty liver diseases (NAFLD) became more prevalent [1, 2]. According to the histopathological findings, NAFLD can be subdivided into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH) [3]. NAFL patients are presented with hepatic steatosis without hepatocyte ballooning injury; while, NASH patients are presented with hepatic steatosis as well as hepatocyte inflammation with or without liver fibrosis)[4].

Accumulating evidence suggested that NAFLD patients have a considerable risk for developing hepatocellular carcinoma even in the absence of liver cirrhosis [5, 6]. In addition, complications resulting from NAFLD are expected to be one of the leading reasons for liver transplantation [7]. Therefore, developing strategies that can aid in the prevention of NAFLD as well as new treatments are a major priority in the field of healthcare research[8]. In the past decades, ursodeoxycholic acid (UDCA) has gained attention for its hepatoprotective effects in liver diseases as well as in NAFLD[9]. UDCA constitutes 3% of total bile acids in the human body[10]. In NAFLD patients, Troisi et al demonstrated that treatment with UDCA for 3 months improved the liver enzymes, liver ultrasound image as well as glycemic control and insulin sensitivity [11]. However, several reports suggested that the beneficial impact of UDCA can be influenced by the patient's own bile acid metabolism [12, 13]. Numerous recent randomized controlled trials (RCTs) have emerged to verify the role of UDCA in NAFLD. Therefore, in this meta-analysis, we aim to present an updated and sensitive qualitative and quantitative analysis for all relevant RCTs [14, 15]. To this end, we gathered all the relevant RCTs and conducted rigorous evaluation to investigate the utility of UDCA in NAFLD in terms of population, age and treatment duration.

Methods

Literature search:

We searched the Web of Science, Pubmed, Embase and Cochrane library databases as well as Chinese articles [16, 17] for RCTs published before March 1, 2019. We used the medical Subject Heading (MeSH) terms and comparable terms in the related databases to screen out articles. The key search terms included: (Acid, Ursodeoxycholic OR Ursacholic Acid OR 3 alpha,7 beta-Dihydroxy–5 beta-cholan–24-oic Acid OR Deoxyursocholic Acid OR Ursolvan OR Delursan OR Destolit OR Sodium Ursodeoxycholate OR Cholofalk OR Ursofalk OR Urso Heumann) AND (Non alcoholic Fatty Liver Disease OR NAFLD OR Nonalcoholic Steatohepatitis OR Livers, Nonalcoholic Fatty OR Steatohepatitides, Nonalcoholic) AND (Randomized OR Randomized controlled trial).

Inclusion and exclusion criteria:

The following inclusion criteria were applied in this study: (1) Only RCTs were included;(2) The intervention group received either UDCA alone or UDCA composite [18]; (3) The control group patients did not receive UDCA; (4) All RCTs participants should be adults with confirmed NAFLD diagnosis [19]; (5) Comparisons between the experimental and control groups should be presented in the form of mean ± standard deviation (SD) or mean ± standard error (SE). On the other hand, studies were be excluded in the following cases: (1) Studies involving pregnant patients or patients younger than 18 years old; (2) Studies with vague or missing outcomes that could not be resolved via email communications; (3) Studies without control group;(4) Studies in which UDCA was combined with other drugs; (5) If the duration of UDCA treatment was less than 8 weeks.

Data extraction:

Two investigators (ZWY and TY) screened the titles and abstracts of all retrieved articles independently. The following data were extracted: design of each study, patient characteristics, number of participants, properties of the study population, geographical location, duration of intervention, year of publication, and mean ± SD (or mean ± SE). In order to minimize the relative heterogeneity, we consider that the duration of intervention to be from baseline till the end of trial (at least 8 weeks). In the case of insufficient or vague data, the corresponding authors were contacted by email twice before excluding the study.

Evaluation of bias:

The risk of bias among the selected trials was evaluated according to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions as described previously [20]. The quality of each trial was assessed in the following 6 aspects: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias. Assessment results were presented as one of three categories: low, unclear or high risk of bias.

Statistical analysis:

We used Stata version 12.0 (Stata Corporation, College Station, TX, USA) for analyzing continuous variables in this study. We used data presented in the form of mean±SD. Data presented as mean± SE were converted to SD using the following formula: mean = mean (after treatment)—mean (baseline); SD = SE × square root n (n: number of participants) and SD = square root [(SD baseline)2 + (SD after-treatment)2 - (2R × SD baseline × SD after-treatment)], the correlation coefficient (R) = 0.5[20]. The results of the meta-analysis are displayed in the form of standardized mean difference (SMD) and 95% confidence interval (CI). Further, Chi-squared and I-square (I 2) tests were calculated to reveal the statistical heterogeneity among the analyzed trials. An I^2 ≥60% indicated moderate heterogeneity, We applied fixed-effect model for analysis; otherwise, the random-effect model was used as detailed previously [21]. SMD values close to 0 ($P > 0.05$) indicated no statistical significance. In contrast, SMD was considered statistically significant when it was away from 0 (P≤0.05). In order to explore the heterogeneity between studies, subgroup analyses were conducted by examining the geographical region, age and duration of intervention as detailed previously [22, 23].

Results

Study features

We collected 134 articles from different data bases in the initial online search. After applying the different inclusion and exclusion criteria，at total of 11 full-text articles including systemic reviews were selected for further screening. Nevertheless, an additional 2 articles were excluded due to insufficient data. Finally, 9 RCTs with 1106 participants were included in this meta-analysis (Figure 1). In addition, pre- and post-treatment serum biochemical parameters are presented in additional file 1:Table S1. Among the enrolled RCTs, two trials were conducted in China[16, 17], one in Korea[18], one in Italy[24], another in

Germany[25], one in Brazil[26], one in the United States [27], another in Turkey [28] and finally one study was conducted in France[29].The duration of intervention ranged from 8 weeks to 24 weeks, and the common form intake of UDCA was through oral administration. The basic characters for the involved trials are summarized shown in Table 1.

Quality assessment:

We evaluated the quality of the included studies by the Cochrane Collaboration's tool [20]. Owing to the different study qualities, the evaluation of each parameter was also unequal. In the random sequence generation, 2 trials demonstrated low risk of bias [18, 24]. A total of 6 trials were at low risk of bias in the Blinding factor [18, 24–27, 29] while the other three studies had unclear risk. For the incomplete outcome data and selective reporting, all 9 trials were at low risk of bias [16–18, 24–29].In addition, all included RCTs (n = 9) ranked unclear risk of bias in the allocation concealment and free of other biases parameters (Table 2).

Meta-analysis:

Compared to the control group (n = 497), our meta-analysis indicated a significant benefit for the use of UDCA in decreasing the serum alanine aminotransferase (ALT) levels in the intervention group (n = 403; SMD = −0.18 at 95% CI [0.32 to −0.05], P = 0.039, I^2 = 50.7%) with inconspicuous heterogeneity. On the other hand, UDCA treatment did not cause a statistically significant reduction in the aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT) levels (SMD = −0.08, 95% CI [−0.22 to 0.05], P = 0.223 and −0.15, 95% CI [−0.45 to 0.14], P = 0.305, respectively; Fig 2–4). Similarly, its impact on the alkaline phosphatase (AP), total bilirubin and albumin in the experimental groups was not significant too (SMD = −0.03, 95%CI [−0.25 to 0.19], P = 0.774; 0.02, 95%CI [−0.16 to 0.21], P = 0.804; and 0.05, 95% CI [−0.16 to 0.25], P = 0.66,respectively). Fig 5–7.

Subgroup analyses:

Next, we carried out subgroup analyses among different subsets: duration of intervention (≤6 months and ⩒6 months), participants' age (≤50 years and ⩒50 years) and geographical region (Asia, Europe and America) (Table 3). Participants from Brazil (South America) [26] and The United States (North America) [27] were categorized into America. Regarding the duration of intervention, our results indicated that longer UDCA treatment duration (⩒6 months) significantly decreased the ALT levels (SMD = −0.24, 95% CI [−0.42 to −0.06], P = 0.008). However, it did not affect the remaining indices. Similarly, patients older than 50 years demonstrated a significant decrease in ALT levels following UDCA administration (SMD = −0.55, 95% CI [−0.89 to −0.22], P = 0.001). The change in ALT levels was not significant among Asian and American populations (SMD = −0.1, 95% CI [−0.32 to 0.11] and −0.05, 95% CI [−0.37 to 0.27], respectively). Interestingly, following UDCA treatment, the change in ALT levels was significant in the European population (SMD = −0.32 95% CI [−0.52 to −0.11], P = 0.003).

Discussion

NAFLD is a chronic liver disorder that affects about 24 % of the adult population worldwide[30]. Therefore, we aimed to analyze and determine the beneficial impact of UDCA treatment among NAFLD patients. In this updated meta-analysis, our results indicated the UDCA treatment can significantly decrease the ALT levels. Further, the subgroup analyses suggested the significant role of UDCA treatment in different geographical regions, age groups and treatment duration. Common complications of NAFLD include type 2 diabetes, cardio-vascular disease and chronic kidney diseases[31].Those complications often result in the development of other chronic conditions thereby, ultimately impacting the patients' quality of life [32]. Mazzella, et al., previously demonstrated that UDCA was more efficient than chenodeoxycholic acid in promoting weight loss [33]. Moreover, its hepatoprotective impact in cholestasis was established and it was attributed to its ability to expel hydrophobic and toxic bile acids [34]. Nevertheless, exploring the applicability of UDCA treatment in hepatobiliary diseases will be instrumental.

In this meta-analysis, we analyzed the impact of UDCA treatment on ALT, AST, GGT, AP, bilirubin and total albumin levels. ALT and AST are liver enzymes that can reflect liver injury or inflammation[35]. GGT is presents in the liver and biliary epithelial cells and it is sensitive marker to hepatobiliary diseases; while, AP levels reflect liver diseases or bones growth issues[36]. Bilirubin is formed by hemoglobin breakdown and high bilirubin concentration often reflects hepatocyte damage thereby causing jaundice. Albumin is made by the liver cells and alteration in albumin levels is an established clinical indication of chronic liver disease [37–39]. Following UDCA administration, significant changes were observed in ALT levels and its subgroups, but changes in the remaining serum biochemical parameters were not significant. This could be possibly attributed to the insufficient number of patients or analyzed parameters among the RCTs. For instance, only 3 trials analyzed the AP[25, 27, 28], albumin[24, 25, 27] and bilirubin[18, 25, 27] levels, respectively. Therefore, analyzing future studies will be required to confirm our current observations.

In this meta-analysis, trials were selected from online databases and previously published systemic reviews [14, 15]. From Orlando et al.'s review [14], we selected only two RCTs due to insufficient data in the other studies [26, 27, 40, 41].Among the 12 clinical trials analyzed by Xiang et al., [15], we were able to extract data from 5 clinical trials only [17, 25, 27–29, 42–48] due to the restriction of our inclusion criteria. Therefore, this study analyzed 7 RCTs [16, 17, 25–29] from the previously published systemic reviews in addition to 2 newly published articles [18, 24].

Ingestion of UDCA was shown to be associated with gastrointestinal adverse effects like diarrhea in three clinical trials [25]. Nevertheless, the other RCTs did not report serious adverse reactions and no significant difference was observed between the UDCA group and the control group. The impact of UDCA on the histological picture was analyzed in few clinical trials; however, we found it difficult to conduct a meta-analysis on the histological findings with a small number of clinical trials [24–28]. Similarly, the small number of enrolled trials hindered our efforts to analyze the publication bias by Funnel plots, Egger's test or Begg's test. Therefore, future meta-analysis will be required to analyze the impact of UDCA with respect to the abovementioned aspects.

Reardon, J et al.[49] did not only report NAFLD in UDCA treatment, but also include alcoholic liver disease (ALD), autoimmune hepatitis (AIH), liver transplant and viral hepatitis,which were demonstrated in the form of table. However, in this study, we only explored the beneficial impact of UDCA administration in NAFLD in order to get rid of bias among other liver diseases. Moreover, our data were conducted by meta-analysis and subgroup analyses, then showed in the form of forest plot and table. To sum up, our results indicated the UDCA treatment can significantly decrease the ALT levels. Aside from the limited number of included studies, this meta-analysis suffered from several limitations. First, complications resulting from NAFLD could interfere with the effects of UDCA. Additionally, all enrolled patients were diagnosed with NAFLD without differentiating between NAFL or NASH patients, which could be a possible source of data bias. Also, the dosage of UDCA varied among the included studies as well as the methods used for evaluation of the final results. Most enrolled studies applied double-blinding, but the details of randomizations were unclear, which contributed the incomplete assessment. Finally, 2 trials were published in non SCI journals which may affect the overall study analysis [16, 17].

Conclusion

In conclusion, our results demonstrate the UDCA was indeed beneficial in lowering the ALT levels among NAFLD patients which promotes the disease recovery. To the best of our knowledge, the impact of UDCA on ALT was not previously published by other meta-analyses. However, more studies are required to thoroughly verify the role of UDCA on the AST, GGT, AP, total bilirubin and albumin levels. Also, the impact of UDCA dosage on chronic liver diseases should be conducted in future studies.

Abbreviations

UDCA = Ursodeoxycholic acid

NAFLD = Nonalcoholic fatty liver disease

NAFL = Nonalcoholic fatty liver

RCTs = Randomized controlled trials

ALT = Alanine aminotransferase

AST = Aspartate aminotransferase

GGT = Gamma-glutamyl transferase

AP = Alkaline phosphatase

NASH = Nonalcoholic steatohepatitis

MeSH = Medical Subject Heading

SD = Standard deviation

SE = Standard error

SMD = Standardized mean difference

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The tables and figures supporting the conclusions of this article are included within the article. There are also one supplementary table online.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

WYZ, QBY and HDH contributed to the conception and design of the study. WYZ and YT conducted the literature search and data extraction, performed the statistical analyses. WYZ, YT and JH drafted the manuscript. HR,YXY, QBY and HDH supervised the study. All authors gave final approval.

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Tables

Due to technical limitations, all Table(s) are only available as a download in the supplemental files section.

Figures

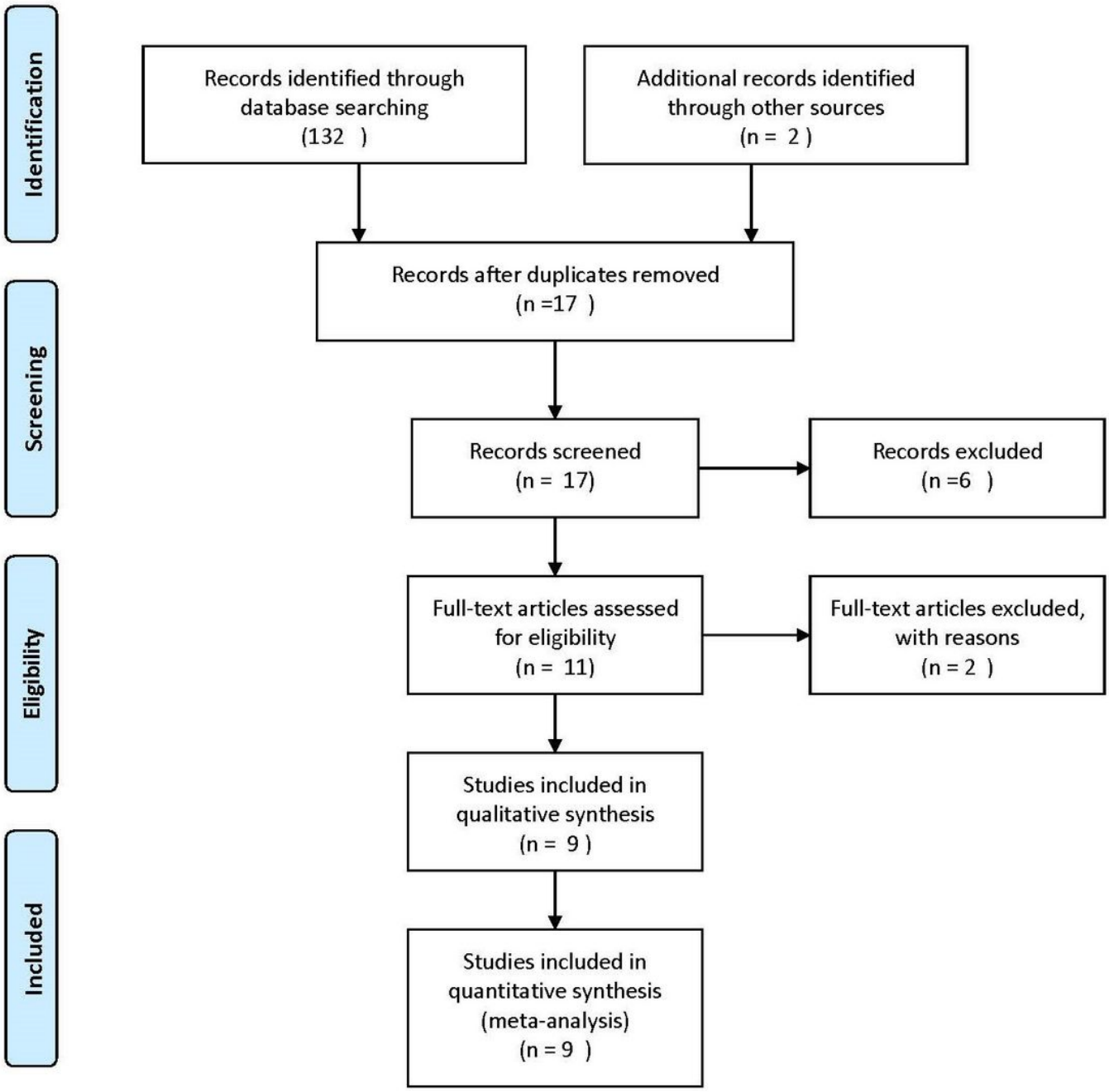

Figure 1

PRISMA flow diagram representing the different phases of this study

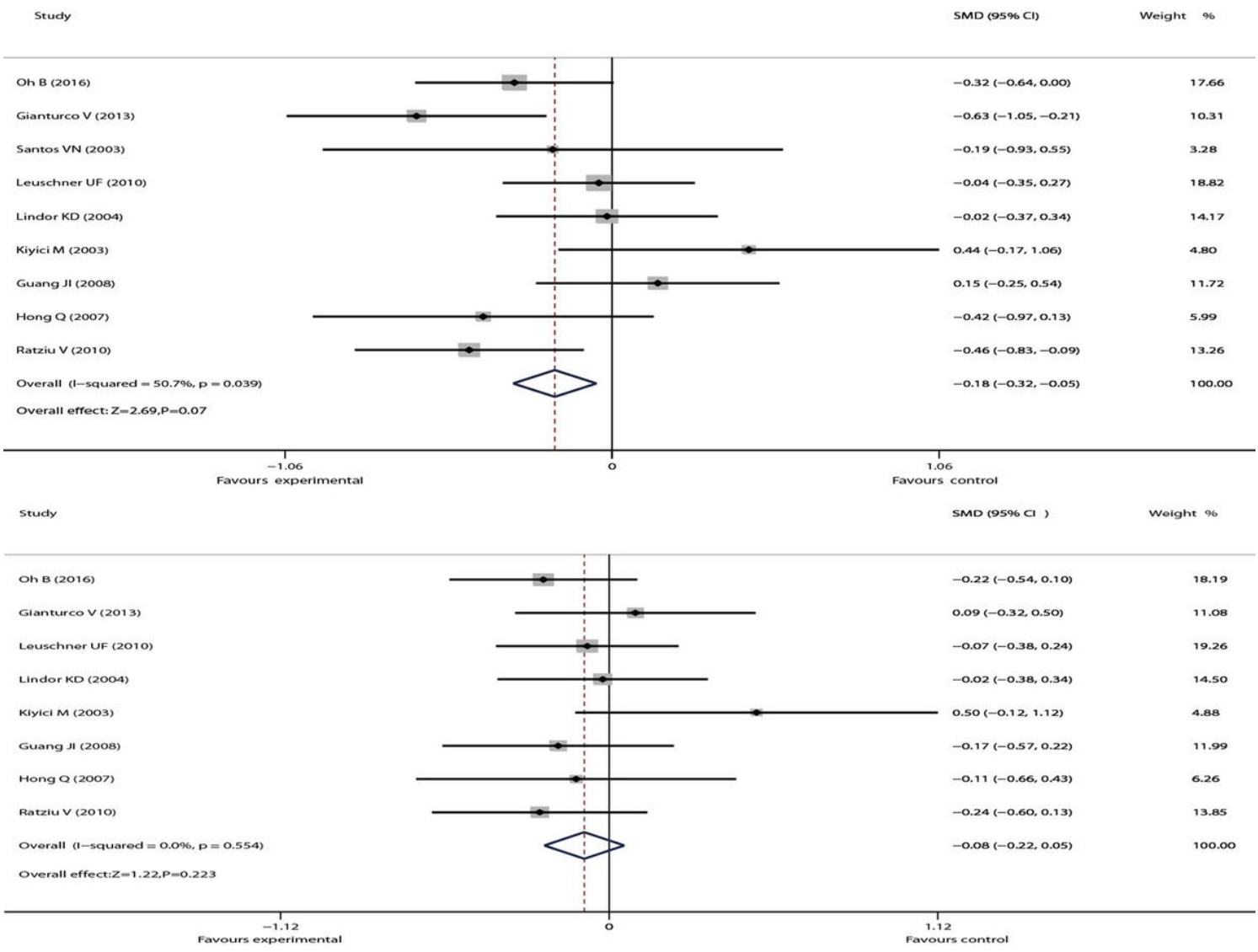

Figure 2

Forest plot of the meta-analysis for comparing experimental with control groups in ALT

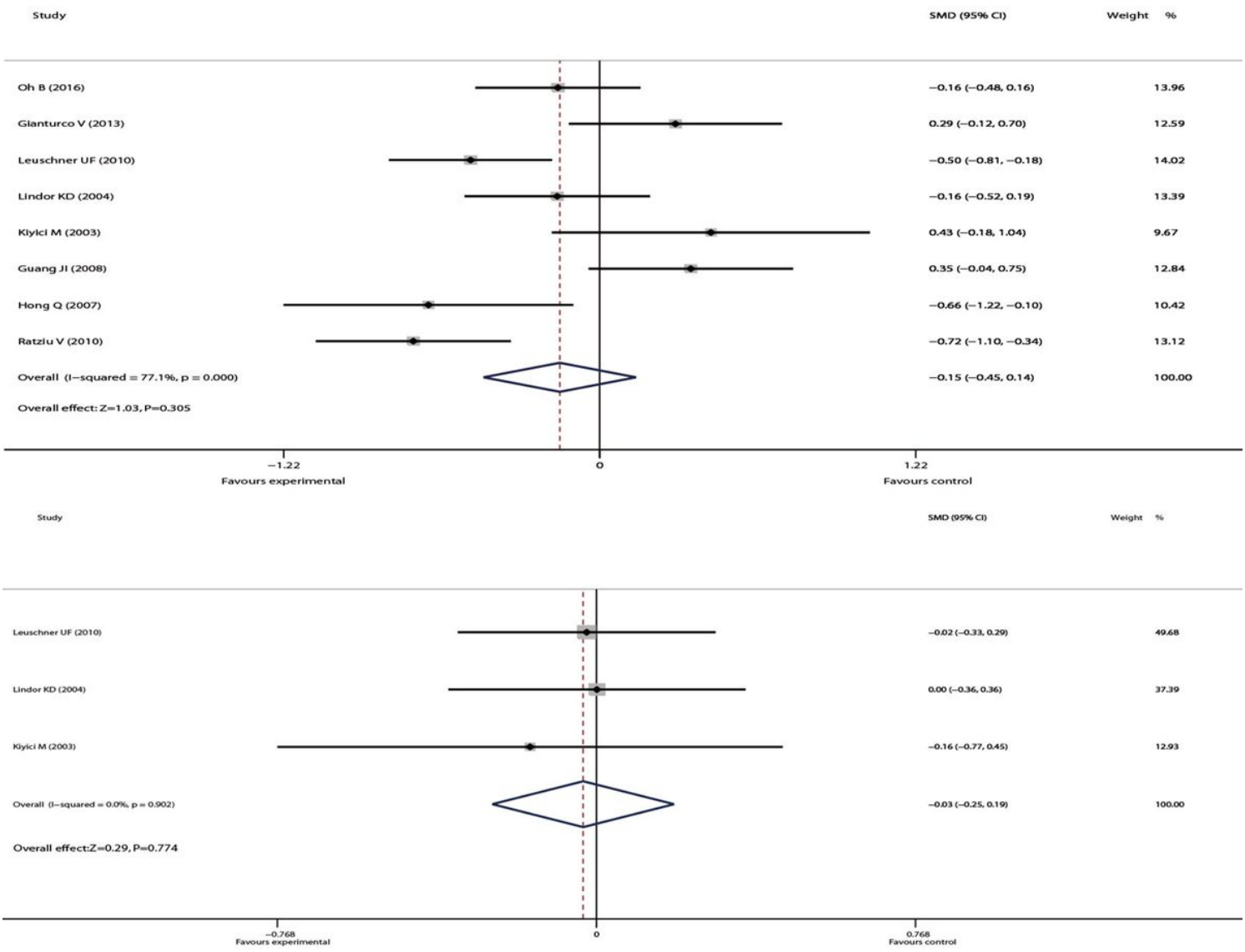

Figure 3

Forest plot of the meta-analysis for comparing experimental with control groups in AST

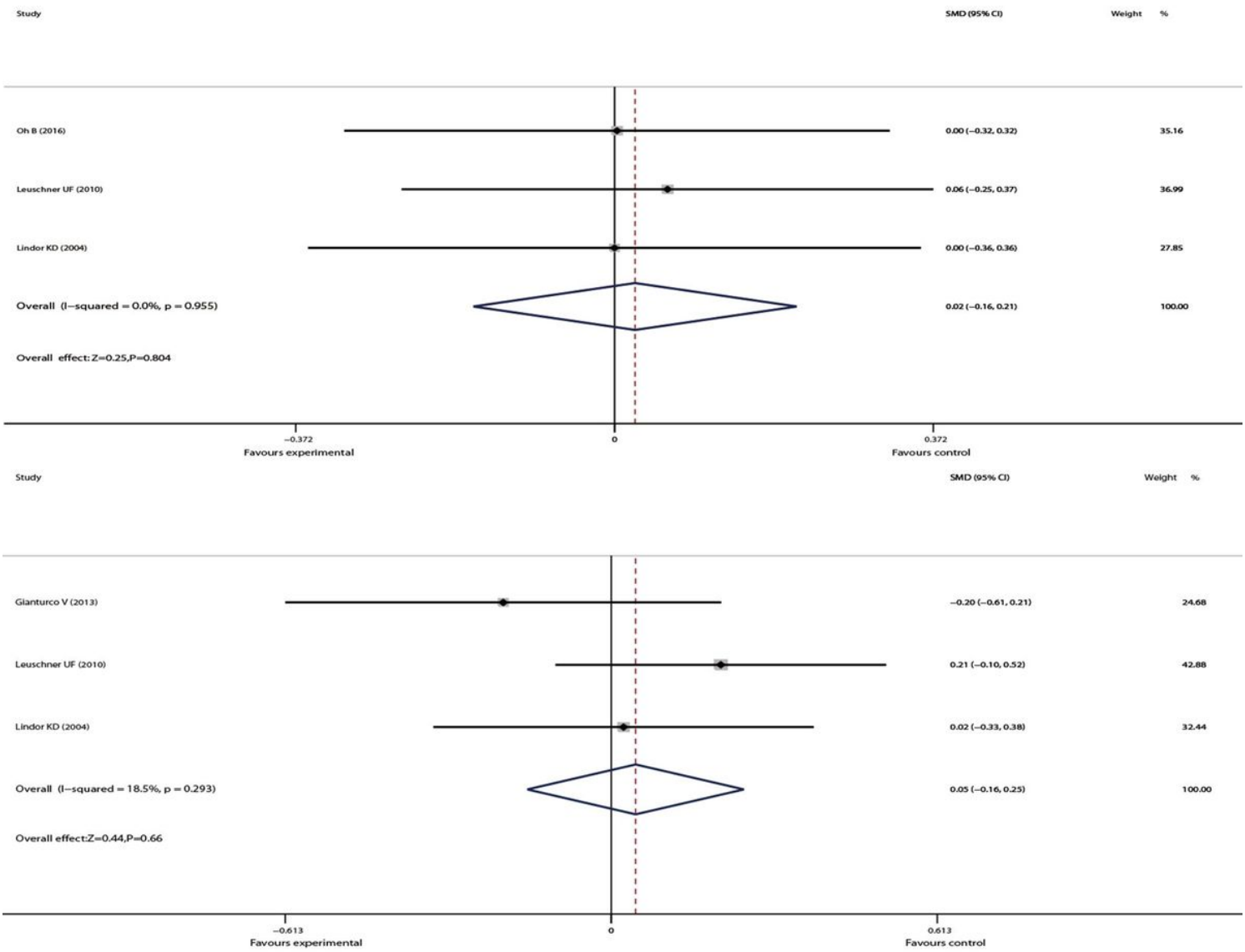

Figure 4

Forest plot of the meta-analysis for comparing experimental with control groups in GGT

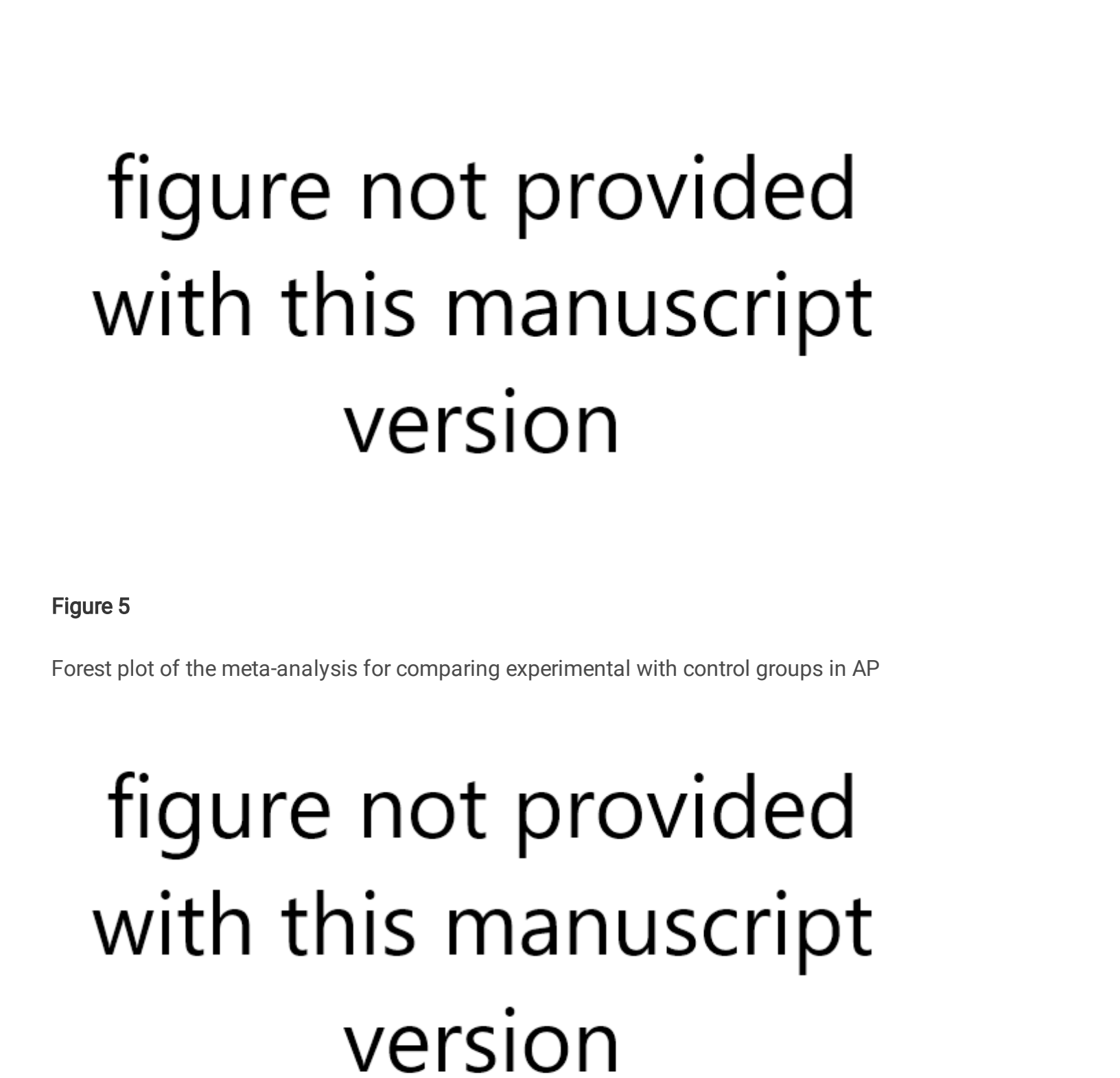

Figure 5

Forest plot of the meta-analysis for comparing experimental with control groups in AP

Figure 6

Forest plot of the meta-analysis for comparing experimental with control groups in total bilirubin

Figure 7

Forest plot of the meta-analysis for comparing experimental with control groups in albumin

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table2.tif
- Table3.tif
- supplementaryadditionnalfile1.doc
- Table1.tif