DR. ALESSANDRO MANTOVANI (Orcid ID : 0000-0002-7271-6329)

DR. ANDREA DALBENI (Orcid ID : 0000-0003-0402-4176)

Article type : Brief Definitive Report

Editor : Jian Sun

Brief Definitive Reports

Coronavirus disease 2019 (COVID-19) and prevalence of chronic liver disease: A meta-analysis

Alessandro Mantovani, MD[1], Giorgia Beatrice, MD[1], Andrea Dalbeni, MD[2]

[1]Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy

[2]Section of General Medicine, Hypertension and Liver Unit, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy

Word count: abstract 148; text 1,692 (including title page, abstract, references); Table n.1; Figure n. 1; Supplementary Table n.1; Supplementary Figure n. 2.

Conflicts of interest: nothing to declare.

Funding: none

Address for correspondence:

Dr. Alessandro Mantovani, MD
Section of Endocrinology, Diabetes and Metabolism
Department of Medicine
University and Azienda Ospedaliera Universitaria Integrata
Piazzale Stefani, 1
37126 Verona, Italy
Phone: +39-0458123110
E-mail: alessandro.mantovani@univr.it

ABSTRACT

At present, there is scarce information regarding the global prevalence of chronic liver disease in individuals with COVID-19 disease, which is become a global pandemic early. Aim of this study was to assess the overall prevalence of chronic liver disease among patients with COVID-19 disease by meta-analyzing data in observational studies and to investigate the relationship between liver damage and COVID-19 disease. We included 11 observational studies for a total of 2,034 adult individuals (median age 49 years [IQR 45-54], 57.2% men). The overall prevalence of chronic liver disease at baseline was 3% (95% CI 2-4%; I^2=29.1%). Individuals with severe COVID-19 disease had relevant alterations of liver enzymes and coagulative profile, probably due to the innate immune response against the virus. Further studies are needed to better investigate the causes of liver injury in patients with COVID-19 disease and the effect of treatment for COVID-19 on the liver.

The novel Coronavirus disease 2019 (COVID-19) is early become a global pandemic with a total of approximately 420,000 confirmed cases, nearly 19,000 confirmed deaths and 197 countries, areas or territories involved (1). These numbers were updated to March 26, 2020 (1). Worldwide, at present, chronic liver disease is a relevant disease burden (2-4). In particular, the most common causes of liver diseases are chronic viral hepatitis, non-alcoholic fatty liver disease and alcohol (2-4). Given this premises, investigating the influence of chronic liver disease on the novel coronavirus disease 2019 is of scientific interest. In fact, accumulating evidence now suggests that patients with severe COVID-19 disease may have higher serum aminotransferase levels when compared to those with non-severe COVID-19 disease and, in some cases, even a significant liver injury (3,4). However, to date, there is still scarce information regarding the global prevalence of chronic liver disease in individuals with COVID-19 disease. Therefore, aim of this study was to assess the overall prevalence of chronic liver disease among patients with COVID-19 disease by meta-analyzing data in the observational studies available so far and to investigate the potential relationship between liver damage and COVID-19.

Studies were selected if they had information on history of chronic liver disease as well as data on serum liver enzymes (i.e., aspartate aminotransferase [AST], alanine aminotransferase [ALT]). No restrictions in terms of race or ethnicity were adopted. Exclusion criteria were: (i) abstracts, reviews, editorials, guidelines; and (ii) studies conducted in pediatric populations. Eleven observational studies (5-15) were identified by systematically searching PubMed (which has a specific section regarding COVID-19 disease) from January 1, 2020 to March 24, 2020 (date last searched) using the free text terms “COVID19” (OR “COVID-19” OR “Coronavirus disease 2019”). Non-English-language papers were excluded. Two investigators (AM and AD) independently examined titles and abstracts and obtained full texts of potentially relevant papers. Working independently, we read the papers and determined whether they met inclusion criteria. Discrepancies were resolved by discussion with a third person (GB). For all eligible studies (5-15), we extracted information regarding study size, source of data, population characteristics and outcome of interest. Data from eligible studies were extracted and meta-analysis was performed using random-effects modeling. All statistical tests were two sided and used a significance level of $p<0.05$. We used STATA® 14.2 (Stata, College Station, TX) for all statistical analyses.

Specifically, *metaprop* command was used for random effect meta-analyses. We used the Score (Wilson) method to compute the confidence intervals.

Table 1 shows the main clinical characteristics of eligible studies. **Supplementary Figure 1** reports the flow diagram of the literature research and study selection. We included eleven observational studies (5-15) for a total of 2,034 (predominantly Chinese) adult individuals (median age 49 years [IQR 45-54], 57.2% [n=1,165] men); 62 of whom had a prior history of chronic liver disease. Ten studies involved Chinese individuals (5-10,12-15), whereas one enrolled US patients (11). Only the study of Arentz *et al.* involved patients over 65 years (11). When reported, the main cause of chronic liver disease was attributed to the infection of hepatic B virus (HBV) or hepatic C virus (HCV). The prevalence of chronic liver disease among eligible case studies is plotted in **Figure 1**. As shown, the overall prevalence of chronic liver disease at baseline was relatively low, being of 3% (95% CI 2-4%; I^2=29.1%). **Supplementary Figure 2** shows the funnel plot of standard error by prevalences of chronic liver disease. The Egger's regression test (p=0.015) showed statistically significant asymmetry for the funnel plot, thus suggesting a potential publication bias (16). Subsequently, we used the non-parametric trim and fill analysis (17), indicating that the impact of publication bias on random effect overall proportion was little (**Supplementary Table 1**).

Among eligible studies, at baseline, mild liver test alterations were observed in most patients with COVID-19, even before the use of various medications (**Table 1**). For instance, regarding serum AST levels the minimum value was 26 IU/L and the maximum value was 46 IU/L. With regard to serum ALT levels the minimum value was 22 IU/L and the maximum value was 41 IU/L. When available, similar considerations can be made for total bilirubin levels and values of prothrombin time (**Table 1**). It is important to note that, when liver function tests for patients with different durations of symptoms were assessed, later presentation was not consistently associated with important alterations of liver function tests (3,4,14). However, when a specific comparison between patients with non-severe COVID-19 disease and those with severe COVID-19 disease was performed (6,7,9,10,13-15), it was possible to note that patients with severe COVID-19 disease tended to have higher levels of liver enzymes, as well as a greater activation of

coagulative and fibrinolytic pathways. For instance, in a recent study of nearly 1,100 Chinese patients, Guan *et al*. documented that elevated serum AST levels were observed in nearly 18% of patients with non-severe COVID-19 disease and in approximately 56% of patients with severe COVID-19 disease (15). Moreover, in that study, elevated serum levels of ALT were also observed in nearly 20% of patients with non-severe COVID-19 disease and in approximately 28% of patients with severe COVID disease (15). Similar findings were also observed in the study of Huang *et al.* (13), where the authors found that patients with severe COVID-19 disease had increased incidence of abnormal liver function.

These observations are in line with the notion that, along with other respiratory viruses that are able to determinate elevations of liver function biomarkers, this novel coronavirus may produce, in some cases, a relevant hepatic damage, probably through the immune interactions requiring the action of intrahepatic cytotoxic T cells and Kupffer cells (2,4). Therefore, seeing the relatively low prevalence of chronic liver disease at baseline in patients with COVID-19, along with other authors (2-4), we suppose that the liver damage observed in those with severe COVID-19 disease is essentially due to a dysregulated innate immune response against the virus rather than to the presence of specific and severe underlying liver diseases. Other coexisting causes for abnormal liver function in patients with severe COVID-19 disease may be the use of hepatotoxic drugs (e.g., acetaminophen) and the development of a systemic inflammatory response or multiple organ dysfunction (2-4).

Our study has some important limitations that should be mentioned. First, the information regarding the prior history of chronic liver disease is not consistently reported in all observational studies on COVID-19 available so far, thereby limiting our ability to select a relevant number of studies. Second, information regarding the causes of chronic liver disease was not available for all eligible observational studies. Third, the individuals included in this study were mainly Chinese and were also relatively young. Therefore, the generalization of our findings to other patient populations should be made with caution.

In conclusion, our study shows that at baseline the prevalence of chronic liver disease is relatively low in patients with COVID-19. However, individuals with severe forms of COVID-19 tend to develop important alterations of liver enzymes and to have changes of coagulative and fibrinolytic pathway profile, due to the innate immune response against the virus. Further studies are needed to better investigate the causes of liver injury in patients with COVID-19 and the effect of treatment for COVID-19 on the liver.

REFERENCES

1. https://www.who.int/emergencies/diseases/novel-coronavirus-2019
2. Feng G, Zheng KI, Yan QQ, Rios RS, Targher G, Byrne CD, Poucke SV, Liu WY, Zheng MH. COVID-19 and Liver Dysfunction: Current Insights and Emergent Therapeutic Strategies. Journal of Clinical and Translational Hepatology 2020;8:1-7.
3. Bangash MN, Patel J, Parekh D. COVID-19 and the liver: little cause for concern. https://doi.org/10.1016/S2468-1253(20)30084-4
4. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol. 2020;S2468-1253(20)30057-1. doi:10.1016/S2468-1253(20)30057-1
5. Mo P, Xing Y, Xiao Y, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan. Clin Infect Dis. 2020;ciaa270. doi:10.1093/cid/ciaa270
6. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China. Clin Infect Dis. 2020;ciaa272. doi:10.1093/cid/ciaa272
7. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan. JAMA. 2020;e201585. doi:10.1001/jama.2020.1585
8. Zhu W, Xie K, Lu H, Xu L, Zhou S, Fang S. Initial clinical features of suspected coronavirus disease 2019 in two emergency departments outside of Hubei, China [published online ahead of print, 2020 Mar 13]. J Med Virol. 2020;10.1002/jmv.25763. doi:10.1002/jmv.25763.

9. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020;e200994.
10. Wan S, Xiang Y, Fang W, et al. Clinical Features and Treatment of COVID-19 Patients in Northeast Chongqing. J Med Virol. 2020;10.1002/jmv.25783. doi:10.1002/jmv.25783
11. Arentz M, Yim E, Klaff L, et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. JAMA. 2020;e204326. doi:10.1001/jama.2020.4326
12. Xu XW, Wu XX, Jiang XG, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series [published correction appears in BMJ. 2020 Feb 27;368:m792]. BMJ. 2020;368:m606. Published 2020 Feb 19. doi:10.1136/bmj.m606
13. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506. doi:10.1016/S0140-6736(20)30183-5
14. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis. 2020;S1473-3099(20)30086-4. doi:10.1016/S1473-3099(20)30086-4
15. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China [published online ahead of print, 2020 Feb 28]. N Engl J Med. 2020;10.1056/NEJMoa2002032. doi:10.1056/NEJMoa2002032
16. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. BMJ 1997; 315: 1533–7.
17. Duval S, Tweedie R. A nonparametric “trim and fill” method of accounting for publication bias in meta-analysis. Journal of the American Statistical Association 2000; 95: 89-98.

FIGURE LEGEND

Figure 1. Forest plot and meta-analysis of prevalences of chronic liver disease in adult patients with COVID-19.

Supplementary Figure 1. The flow diagram of the literature research and study selection.

Supplementary Figure 2. Funnel plot of standard error by prevalences of chronic liver disease.

Table 1. Main characteristics of observational studies on COVID-19 disease with information on history of chronic liver disease.

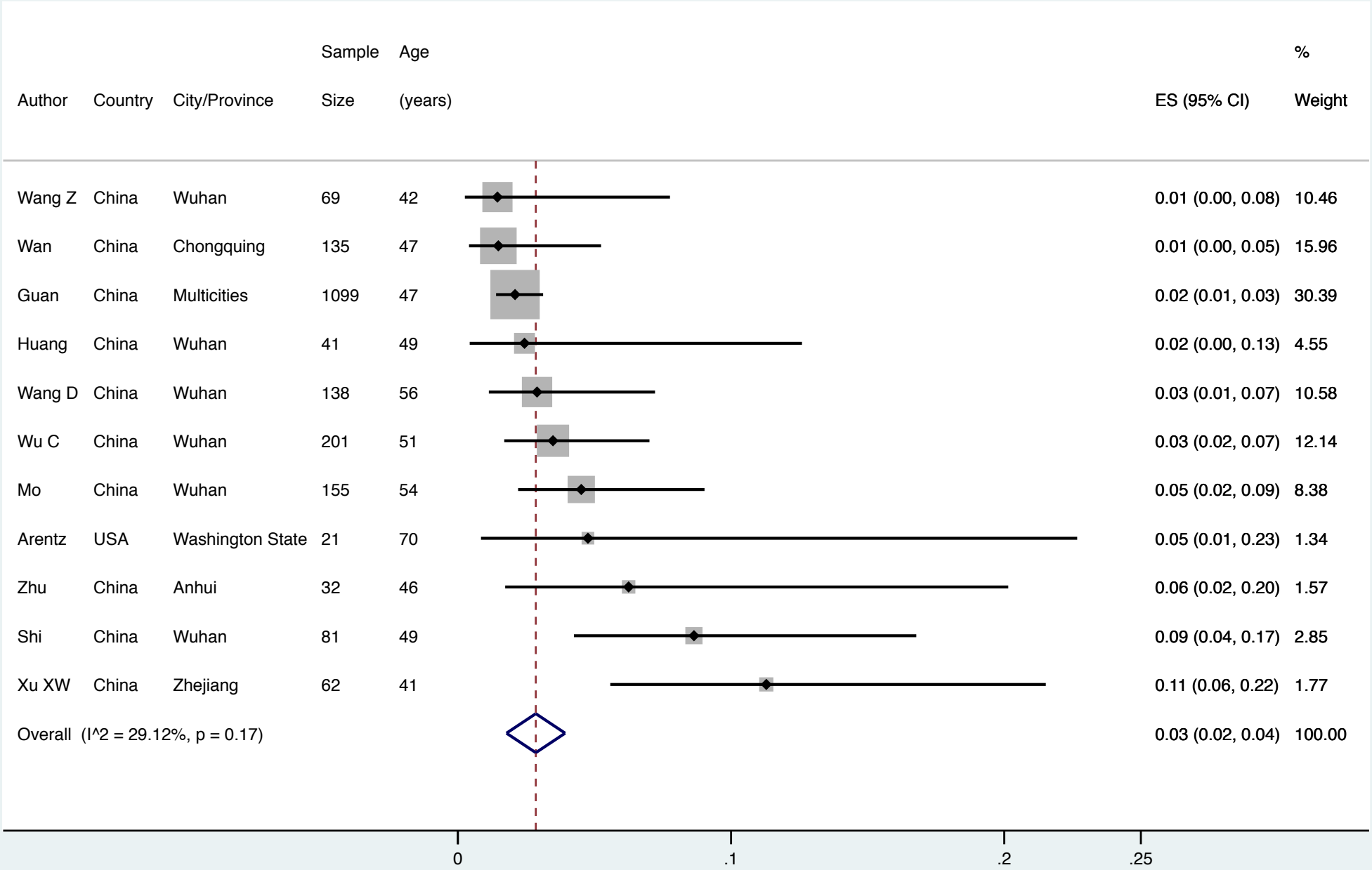
Author [Ref.]	PMID	Country	City/Province	Sample size	Age (years)	AST (IU/L)	ALT (IU/L)	Total Bilirubin (mg/dl)	Protrombine time (s)	Notes
Mo et al [5]	32173725	China	Wuhan	155	54	32 (24-48)°	23 (16-38)°			None
Wang Z et al [6]	32176772	China	Wuhan	69	42	28 (22-42)°	25 (17-40)°			Patients with severe disease had higher serum levels of AST [40 IU/L (95% CI 24-62)] than those with non-severe disease AST [26 IU/L (95% CI 21-39)]. Almost identical findings were also observed for ALT levels
Wang D et al [7]	32031570	China	Wuhan	138	56	31 (24-51) °	24 (16-40)	9.8 (8.4-14.1)[**]	13.0 (12.3-13.7) °	Patients admitted to ICU care had higher serum levels of AST [52 IU/L (95% CI 30-70)] and ALT [35 IU/L 95% 19-57)] than those not admitted to ICU care [i.e., AST: 29 IU/L (95% CI 21-38)]; ALT 23 IU/L (95% CI 15-36)]. Similar findings

										were also observed for total bilirubin levels
Zhu etl al [8]	32167181	China	Anhui	32	46	31±16[§]	30.1±31.2			Only diagnosed patients were considered here
Wu C et al [9]	32167524	China	Wuhan	201	51	33 (26-45)°	31 (20-47)	11.4 (9.0-14.7)°	11.1 (10.2-11.9)°	Patients with ARDS had higher serum levels of AST (38 IU/L [95% CI 30-53]) than those without ARDS [30 IU/L (95% CI 24-38)]. Similar findings were also observed for ALT levels. No differences were observed when patients with ARDS were further stratified by survivors and non-survivors
Wan et al [10]	32198776	China	Chongquing	135	47	33 (28-44)°	26 (13-33)	8.6(5.9-13.7)[°*]	10.9 (10.5-11.4)°	Patients with severe disease had higher serum levels of AST (34 IU/L [95% CI 26-44]) than those with mild disease [AST: 22 IU/L (95% CI 17-30)]. Similar findings were also observed for ALT levels
Arentz et al [11]	32191259	USA	Washington State	21	70			0.6 (0.2-1.1) °		Patients admitted to ICU care

Xu XW et al [12]	32075786	China	Zhejiang	62	41	26 (20-32) °	22 (14-34)			Serum levels of AST increased in 10 (16%) patients.
Huang et al. [13]	31986264	China	Wuhan	41	49	34 (26-48) °	32 (21-50)°		11.1 (10.1–12.4)°	Among patients admitted to ICU care, the prevalence of individuals with higher serum levels of AST (i.e., >40 IU/L) was 62%. By contrast, among patients not admitted to ICU care, the prevalence of individuals with higher serum levels of AST was 25%.
Shi et al. [14]	32105637	China	Wuhan	81	49	46±18§	41±29§	11.9±3.6§	28.9±8.4§	No differences in terms of serum levels of AST and ALT where observed when the patients were stratified by the time interval between onset of symptoms and the computed tomography scan
Guan et al. [15]	32109013	China	Multicities	1099	47					Among patients with severe disease, the prevalence of individuals with higher

										serum levels of AST and ALT (i.e., >40 IU/L) was 39% and 28%, respectively. By contrast, among patients with no-severe disease, the prevalence of individuals with higher serum levels of AST and ALT was 18% and 20%, respectively

Abbreviations: AST: aspartate aminotransferase; ALT: alanine aminotransferase; ICU: intensive care unit. °Data are expressed as median and interval interquartile (in parenthesis). §Data are expressed as mean±SD. *umol/L


Author
Country
City/Province
Sample Size
Age (years)
ES (95% CI)
% Weight
Wang Z China Wuhan 69 42 0.01 (0.00, 0.08) 10.46
Wan China Chongquing 135 47 0.01 (0.00, 0.05) 15.96
Guan China Multicities 1099 47 0.02 (0.01, 0.03) 30.39
Huang China Wuhan 41 49 0.02 (0.00, 0.13) 4.55
Wang D China Wuhan 138 56 0.03 (0.01, 0.07) 10.58
Wu C China Wuhan 201 51 0.03 (0.02, 0.07) 12.14
Mo China Wuhan 155 54 0.05 (0.02, 0.09) 8.38
Arentz USA Washington State 21 70 0.05 (0.01, 0.23) 1.34
Zhu China Anhui 32 46 0.06 (0.02, 0.20) 1.57
Shi China Wuhan 81 49 0.09 (0.04, 0.17) 2.85
Xu XW China Zhejiang 62 41 0.11 (0.06, 0.22) 1.77
Overall (I^2 = 29.12%, p = 0.17) 0.03 (0.02, 0.04) 100.00
0
.1
.2
.25