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MINIREVIEWS

Chronic hepatitis B-associated liver disease in the context of human immunodeficiency virus co-infection and underlying metabolic syndrome

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Abstract

Globally, a shift in the epidemiology of chronic liver disease has been observed. This has been mainly driven by a marked decline in the prevalence of chronic hepatitis B virus infection (CHB), with the greatest burden restricted to the Western Pacific and sub-Saharan African regions. Amidst this is a growing burden of metabolic syndrome (MetS) worldwide. A disproportionate co-burden of human immunodeficiency virus (HIV) infection is also reported in sub-Saharan Africa, which poses a further risk of liver-related morbidity and mortality in the region. We reviewed the existing evidence base to improve current understanding of the effect of underlying MetS on the development and progression of chronic liver disease during CHB and HIV co-infection. While the mechanistic association between CHB and MetS remains poorly resolved, the evidence suggests that MetS may have an additive effect on the liver damage caused by CHB. Among HIV infected individuals, MetS-associated liver disease is emerging as an important cause of non-AIDS related morbidity and mortality despite antiretroviral therapy (ART). It is plausible that underlying MetS may lead to adverse outcomes among those with concomitant CHB and HIV co-infection. However, this remains to be explored through rigorous longitudinal studies, especially in sub-Saharan Africa. Ultimately, there is a need for a comprehensive package of care that integrates ART programs with routine screening for MetS and promotion of lifestyle modification to ensure an improved quality of life among CHB and HIV co-infected individuals.

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Core Tip: Independently, chronic hepatitis B virus (HBV) infection, human immunodeficiency virus (HIV) infection and metabolic syndrome (MetS) are known risk factors of chronic liver disease. The presence of MetS components, including type 2 diabetes mellitus, central obesity and lipid abnormalities, are associated with adverse outcomes and altered treatment response among HBV and HIV infected individuals. While underlying MetS may have an additive effect on the development and progression of chronic liver disease among HBV-HIV co-infected individuals, the evidence from endemic regions like sub-Saharan Africa is limited and deserves further attention in the research agenda.

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INTRODUCTION

Chronic liver disease is a frequent clinical condition accounting for an estimated 2 million deaths each year worldwide[1]. It is characterized by a progressive deterioration of liver function, involving a continuous process of inflammation, destruction and regeneration of the cells of the liver. This often leads to complications such as liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC). A broad spectrum of etiologies is associated with chronic liver disease and typically includes alcohol use disorder, chronic exposure to toxins, viral hepatitis including chronic hepatitis B virus (HBV) infection and immune and metabolic disorders[1]. Globally, an epidemiological shift in the burden of chronic liver disease has been observed, mainly driven by diabolical factors. On the one hand are the global efforts that have led to the increased elimination of aflatoxins from food, improved safety of transfusions and transplantations, the establishment of viral hepatitis treatment programs and universal childhood hepatitis B vaccination programs; and on the other hand is the increasing burden of metabolic disorders worldwide and the persisting endemicity of chronic HBV infection (CHB) in regions such as the Western Pacific and sub-Saharan Africa[1-3].

It is well established that CHB is a leading cause of liver disease and death worldwide. The World Health Organization estimates that currently 257 million persons or 3.5% of the world's population are chronic carriers of HBV, 68.0% of whom live in the Western Pacific (115 million) and sub-Saharan African (60 million) regions alone[4]. The greater proportion of chronic carriers are persons who were born prior to the establishment of universal childhood hepatitis B vaccination programs. What further compounds the situation in a region like sub-Saharan Africa is the fact that it is also home to 71.0% of the global population (35 million) of people living with human immunodeficiency virus (PLHIV)[5,6]. Due to similar routes of transmission, co-infection with HBV and HIV are not uncommon. Of the 2.7 million HBV-HIV co-infected persons worldwide, 69.0% or 1.9 million live in sub-Saharan Africa[7]. With rapid expansion of antiretroviral treatment (ART) programs, there has been a dramatic decline in AIDS-related deaths and consequently an increase in the life expectancy of PLHIV, including those co-infected with HBV[5,6]. However, as PLHIV are living longer, an increased risk of chronic liver disease has been observed and is emerging as an important cause of non-AIDS-related mortality within this population[8,9]. Among PLHIV, liver-related mortality has been found to be up to 10 times of that occurring within the general population[10]. Development of chronic liver disease among PLHIV has been associated with underlying viral hepatitis (including CHB) and non-viral hepatitis risk factors such as lifelong exposure to components of ART regimens with hepatotoxic effects and the development of metabolic syndrome (MetS)[8].

MetS is a common yet complex condition characterized by a clustering of various metabolic disorders (Table 1) that are known to increase the risk of developing chronic liver disease or to worsen the prognosis among individuals with other underlying risk factors of chronic liver disease[11-14]. Chronic liver disease among individuals with MetS is often preceded by the accumulation of fats or triglycerides in the cells of the liver due to MetS components like insulin resistance, abnormal lipid metabolism and dysregulation of cytokines and adipokines, leading to a spectrum of fatty liver disorders known as non-alcoholic fatty liver disease (NAFLD). With significant liver inflammation and injury over time, a severe form of NAFLD develops, referred to as non-alcoholic steatohepatitis (NASH). NASH is associated with liver damage and progression to advanced liver cirrhosis and fibrosis[15]. The evidence on the association between MetS and other common risk factors of chronic liver disease, such as CHB, is oftentimes conflicting. In addition, the role of MetS in the development and prognosis of chronic liver disease among HBV-HIV co-infected individuals is unclear. With the concomitant high burden of CHB and HIV infection, and the growing prevalence of MetS and its associated complications, sub-Saharan Africa presents a unique case for continuously examining key risk factors of chronic liver disease in order to inform ongoing public health interventions[16].

We review evidence emerging over the last decade (2010-2020) to improve current understanding of the pathogenesis of chronic liver disease among CHB and HIV co-infected individuals with underlying MetS. We identify gaps in the evidence base and propose recommendations for future research, as well as current policy and practice. This review takes a special focus on sub-Saharan Africa where the burden of CHB and HIV co-infection is high, the prevalence of MetS is growing and the need for intervention is often the greatest.

CONFLICTING EVIDENCE ON THE ASSOCIATION BETWEEN METS AND CHB

With 6.1% of the population living with CHB, the burden of liver cirrhosis, fibrosis and HCC in sub-Saharan Africa is significant[4]. The association between MetS and the increased risk of chronic liver disease presents an added burden and calls for greater attention within this population. Despite this, our review of primary studies published within the last decade reveal a profound lack of data on CHB and MetS from sub-Saharan Africa.

Drawing on data from elsewhere, the combined prevalence of MetS among those with CHB varies from 5.0% to 30.1%[17,18]. In Europe, studies conducted in Slovakia report MetS prevalence rates of 27.8% among Roma[19] and 24.6% among both Caucasian and Roma[20] populations with CHB. This is comparable to findings from a study conducted in Spain that found that 24.0% of individuals with CHB had underlying MetS[21]. In both Slovakian studies, however, no significant association between MetS and HBV infection was found, as the prevalence of the condition was comparable between those with or without CHB (27.8% in CHB patients *vs* 29.6% in controls, $P = 0.785$[19]; and 24.6% in CHB patients *vs* 24.7% in controls, $P = 0.561$[20]), irrespective of age and sex. Instead, the studies did show that CHB patients with MetS presented with significantly higher HBV-DNA viral load and elevated liver enzymes, including alanine aminotransferase (ALT) and gamma-glutamyl transferase, compared to those without MetS, suggesting an additive effect of MetS on the liver damage caused by CHB[19,20]. Contrary to these findings, a large population-based study conducted in the United States (the NHANES III study) described a significantly lower prevalence of MetS in CHB patients compared to controls (10.4% *vs* 25.6%, $P = 0.019$). Stratified by sex, this inverse correlation between MetS and CHB was found to persist in males but not in females[22]. Unlike the Slovakian observations, CHB patients with high levels of ALT in the NHANES III study had a significantly lower rate of MetS compared with controls (2.1% *vs* 49.8%, $P < 0.001$). Given these findings, the authors hypothesized that chronic liver inflammation, instead of HBV itself, may be responsible for metabolic derangements in CHB patients[22]. It is worth noting that participants in the NHANES III study were relatively older than those in the Slovakian studies, and this may have influenced the conflicting findings. Evidence emerging from Asia on the association between CHB and MetS is no less conflicting than that discussed previously. For example, a case-series conducted in Taiwan found no correlation between CHB and MetS[23], while two other cross-sectional studies from Taiwan reported an inverse correlation between CHB and MetS[24,25]. Contrary to this, a positive association between latent HBV infection and MetS [hazard ratio (HR) = 2.27,

Table 1 Metabolic syndrome—definition, diagnostic criteria and association with chronic liver disease

Definition of MetS

A clustering of metabolic disorders that include hypertension, central obesity, impaired glucose metabolism including insulin resistance and abnormal cholesterol or triglyceride levels. MetS increases the risk of morbidity and mortality from cardiovascular disease, stroke, type 2 diabetes, chronic kidney disease and chronic liver disease

Diagnostic criteria[1]

NCEP/ATP III[27]	AHA/NHLBI[28]	IDF[29]	JIS[30]	WHO[31]
Presence of ≥ 3 of the following:	Presence of ≥ 3 of the following:	Central obesity; ethnicity-specific waist circumference values[2] or BMI > 30 kg/m^2 plus any 2 of the following:	Presence of ≥ 3 of the following:	Glucose intolerance, impaired glucose tolerance or diabetes mellitus and/or insulin resistance and any 2 of the following:
Abdominal obesity; > 102 cm in males and > 88 cm in females	Elevated waist circumference; ≥ 102 cm in males and ≥ 88 cm in females	Raised triglycerides; ≥ 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality	Elevated waist circumference; population- and country-specific definitions[2]	Raised arterial pressure; ≥ 160/90 mmHg
Elevated triglycerides; ≥ 150 mg/dL or treatment for elevated triglycerides	Elevated triglycerides; ≥ 150 mg/dL (1.7 mmol/L) or treatment for elevated triglycerides	Reduced HDL cholesterol; < 40 mg/dL (1.03 mmol/L) in males and < 50 mg/dL (1.29 mmol/L) in females, or specific treatment for this lipid abnormality	Elevated triglycerides; ≥ 150 mg/dL (1.7 mmol/L) or treatment for elevated triglycerides	Raised plasma triglyceride; ≥ 150 mg/dL, and/or low HDL cholesterol; < 35 mg/dL in males and < 39 mg/dL in females
Reduced HDL cholesterol; < 40 mg/dL in males and < 50 mg/dL in females	Reduced HDL cholesterol; < 40 mg/dL (1.03 mmol/L) in males and < 50 mg/dL (1.3 mmol/L) in females or treatment for reduced HDL cholesterol	Raised blood pressure; ≥ 130/≥ 85 mmHg, or treatment of previously diagnosed hypertension	Reduced HDL cholesterol; < 40 mg/dL (1.0 mmol/L) in males and < 50 mg/dL (1.3 mmol/L) in females, or treatment for reduced HDL cholesterol	Central obesity; waist/hip ratio > 0.90 in males and > 0.85 in females and/or BMI > 30 kg/m^2
Elevated blood pressure; ≥ 130/≥ 85 mmHg or treatment for elevated blood pressure	Elevated blood pressure; ≥ 130/≥ 85 mmHg or antihypertensive treatment	Raised fasting plasma glucose; ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes	Elevated blood pressure; ≥ 130/≥ 85 mmHg or anti-hypertensive treatment	Microalbuminuria; urinary albumin excretion rate ≥ 20 μg/min or albumin/creatinine ratio ≥ 20 μg/mg
Elevated fasting glucose; ≥ 110 mg/dL or treatment for elevated glucose	Elevated fasting glucose; ≥ 100 mg/dL or treatment for elevated glucose		Elevated fasting glucose; ≥ 100 mg/dL, or treatment of elevated glucose	

MetS and chronic liver disease

The association between MetS and chronic liver disease involves a complexity of risk factors which are yet to be fully understood. NAFLD which covers a spectrum of fatty liver disorders including NASH, is the most common cause of abnormal liver function among individuals with MetS. MetS components like insulin resistance may increase fatty acids in the liver, leading to fat or triglyceride accumulation in hepatocytes. NASH, which is an advanced form of NAFLD, is associated with liver inflammation and liver damage, leading to the development of liver cirrhosis and progression to advanced liver fibrosis. In addition, type 2 diabetes and obesity may increase the risk of HCC. The presence of MetS may have worse outcomes in individuals with other causes of chronic liver disease, such as viral hepatitis.

[1]NCEP/ATP III: National Cholesterol Education Program/Adult Treatment Panel III; AHA/NHLBI: American Heart Association/National Heart, Lung and Blood Institute; IDF: International Diabetes Federation; JIS: Joint Interim Statement; WHO: World Health Organization.

[2]Currently, ethnicity-specific waist circumference values have not been defined for populations from sub-Saharan Africa. BMI: Body mass index; HCC: Hepatocellular carcinoma; HDL: High-density lipoprotein; MetS: Metabolic syndrome; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis.

95%CI: 1.52-3.38] was demonstrated in a retrospective cohort study conducted in China, suggesting that latent HBV infection may be a risk factor for the development of MetS[26].

Evidently, the mechanistic association between CHB and MetS remains poorly

resolved. Reasons for the conflicting findings may include variations in the MetS diagnostic criteria used in the various studies (Table 1)[27-31]. The geographic heterogeneity of the published data also means that a comparison between studies may not always be feasible. Also, worth noting is the fact that a majority of the published studies are cross-sectional in nature, which often draws the weakest evidence for the establishment of causal associations between CHB and MetS, as opposed to robust longitudinal studies. Despite the disparities in the prevalence of MetS reported among those with CHB, the evidence base strongly suggests that older age[24] and female sex[18,25,32,33] may be predictors of MetS within this population.

Several studies have shown that underlying MetS increases the risk and progression of liver fibrosis, cirrhosis and HCC in patients with CHB[17,34-36]. A longitudinal population-based study involving 2979 participants aged 40-65 years, of whom 1690 had CHB, revealed that the presence of three or more metabolic risk factors, compared with no factors, significantly increased the risk of HCC by two- to three-fold among CHB patients[36]. This relationship persisted after controlling for viral factors such as high HBV-DNA viremia (≥ 10000 copies/mL) and other known risk factors of HCC[36]. These findings are consistent with observations made elsewhere[34]. Among these metabolic risk factors, insulin resistance and central obesity are independently associated with the development of liver damage and HCC. In a longitudinal cohort study conducted by Huang *et al*[37], a significantly higher cumulative incidence of cirrhosis [log-rank test, $P < 0.001$, with a relative risk (RR) of 3.43, 95% confidence interval (CI): 2.62-4.49] and decompensated cirrhosis (log-rank test, $P < 0.001$, with an RR of 4.11, 95%CI: 2.95-5.70) was noted among CHB patients with newly diagnosed diabetes as compared to those without diabetes. Adjusting for age, sex, CHB treatment, HCC and comorbidity index, type 2 diabetes mellitus (T2DM) remained an independent predictor for cirrhosis (HR = 2.015; 95%CI: 1.393-2.915; $P < 0.001$) and decompensated cirrhosis (HR = 1.792; 95%CI: 1.192-2.695; $P = 0.005$)[37]. Another study showed that pre-existing T2DM for > 5 years before cirrhosis diagnosis, insulin and/or sulphonylurea use and poor diabetic control (defined as glycated hemoglobin A1c ≥ 7.0%) were predictors of cirrhosis complications and HCC development[38]. These findings were confirmed by a longitudinal study that reported a significantly higher incidence of HCC (13.3% *vs* 10.0%; $P < 0.001$) and HCC-related mortality (7.5% *vs* 4.7%; $P < 0.001$) among 2966 CHB patients with T2DM compared to 2966 CHB patients without T2DM, after a median follow-up of 11.4 years[39]. Elevated serum adiponectin levels may also play a role in the increased risk of liver fibrosis, cirrhosis and HCC[40,41].

When investigating dyslipidemia, including hypercholesterolemia or hypertriglyceridemia, among CHB patients *vs* controls, several studies have reported significantly lower levels of total cholesterol and triglycerides among those with CHB[19,20,42,43]. Among CHB patients, significant disparities have been observed in the levels of triglycerides, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) detected among males *vs* females and those aged ≤ 45 years *vs* > 45 years[18,23,32]. While the heterogeneity in the lipid profiles detected among CHB patients is not fully understood, some virus-specific risk factors have been linked with the lipid abnormalities observed within this population. For example, HBV infection is known to cause liver injury, which may lead to impaired liver function, thereby altering total cholesterol and triglyceride levels[42]. Moreover, it has been shown that the viral HBx protein inhibits the secretion of apolipoprotein B, which is an essential component for the formation of very-LDL and LDL, thereby lowering serum triglyceride levels and causing the accumulation of hepatic triglycerides[43,44]. This is particularly concerning as excessive accumulation of triglycerides in the liver leads to NAFLD.

Both CHB and NAFLD are recognized as significant causes of liver cirrhosis and fibrosis. Thus, it is only reasonable to examine the relationship between these conditions. Several studies have reported a positive association between hepatic steatosis and MetS components such as high body mass index or central obesity, elevated serum triglyceride and total cholesterol levels and insulin resistance, among those with CHB[45-47], although an inverse relationship with HBV replication and hepatitis B surface antigen positivity has also been reported[46,48-50]. These observations suggest host factors, and not HBV itself, as predictors of hepatic steatosis in those with CHB. Interestingly, Joo *et al*[51] found that HBV infection was significantly associated with a lower risk of incident NAFLD. By investigating the lipid profiles in these patients, the authors reported a significant decrease in total cholesterol levels over time among CHB patients compared with controls, suggesting that HBV infection could protect against the development of NAFLD, possibly through its effect on lipid metabolism.

SUBSTANTIAL BURDEN OF METS AND NAFLD AMONG PLHIV

Sub-Saharan Africa has a disproportionate burden of HIV infection, and there is evidence to suggest that a significant proportion of PLHIV within this region are at increased risk of developing MetS and its associated complications, including chronic liver disease[13,52]. It is worth noting however, that the true burden of MetS among PLHIV in sub-Saharan Africa is often difficult to ascertain, given the heterogeneity of the condition itself, the lack of ethnicity-specific diagnostic criteria for sub-Saharan African populations and the disparities in the associated risk factors (HIV-related *vs* host and environmental-related risk factors). Table 2 shows the variable prevalence rates of MetS among PLHIV from selected studies conducted in sub-Saharan African countries within the last decade[53-67]. These variations in the prevalence of MetS among PLHIV are not exclusive to sub-Saharan African countries but have been reported in similar population groups in Latin America[68] and Europe[69-72]. The commonly reported independent risk factors associated with MetS among PLHIV in sub-Saharan Africa include female sex, age > 40 years and central obesity[56,59,62]. The potential influence of host genetics in the development of MetS within this population has also been suggested previously[66].

A persistent matter of debate in the evidence-base has been the impact of lifelong exposure to ART on the burden of MetS among PLHIV. In a recent cross-sectional study conducted among PLHIV in Ghana, Obirikorang *et al*[65] found a higher prevalence of MetS among participants on ART compared to their ART-naïve counterparts, irrespective of the diagnostic criteria used. Consistent with this finding, a study conducted in Cameroon reported prevalence rates of 36.0% and 23.4% among those on ART compared to ART-naive individuals, respectively[57]. Mbunkah *et al*[60] further reported statistically significant (P = 0.02) variations in MetS prevalence among those on first-line ART (24.2%) and second-line or protease inhibitor-based ART (10.0%), compared to ART-naive (11.5%) Cameroonian PLHIV. Contrary to these findings, Ngatchou *et al*[63] found that ART-naïve individuals rather experience a two-fold increase in the prevalence of MetS, suggesting a possible influence of uncontrolled HIV replication, while Tesfaye *et al*[67] noted that the prevalence of MetS among PLHIV in Ethiopia was not influenced by whether or not they had initiated ART. To date, the findings from sub-Saharan Africa have been limited by the cross-sectional design adopted by most studies. Findings from a previous longitudinal study conducted in Italy show that after 3 years of follow-up, there was no significant difference in the incidence of MetS among those on ART and ART-naïve individuals. Instead, the authors posit that there may be different metabolic pathways underlying the development of MetS in ART-naïve individuals compared to those on ART[72]. While the findings on MetS among PLHIV in sub-Saharan Africa remain inconclusive, they do suggest a possible multi-factorial mechanism—involving viral, host and environmental factors—underlying the pathogenesis of MetS among PLHIV, which underscores the importance of the condition within this population.

Historically, the development of chronic liver disease among PLHIV has been associated with concomitant viral hepatitis, ART-associated hepatotoxicity and alcoholic liver disease[8]. Emerging evidence now shows that NAFLD is increasingly becoming an important cause of significant liver morbidity among PLHIV[73-75]. Unfortunately, evidence emerging from sub-Saharan Africa on the burden of NAFLD among PLHIV is limited, and this has been raised previously as a regional public health concern[76]. Our search for relevant sub-Saharan African studies published within the last decade on this topic returned only one output from South Africa that reported a hepatic steatosis prevalence rate of 28.0% among PLHIV[77]. This is considerably lower than prevalence rates reported for Asian populations (31.0%)[78] as well as from studies conducted in Canada (54.0%)[79] and Greece (55.0%)[80]. These studies also provide strong evidence suggesting that PLHIV are at high risk for developing NASH, fibrosis and HCC, spurred by a high burden of traditional MetS components such as insulin resistance, central obesity and dyslipidemia[78-81]. Several reports from sub-Saharan Africa do indicate that these traditional MetS components (insulin resistance, T2DM, central obesity and dyslipidemia) are in fact prevalent among PLHIV, which could suggest a significant risk for the development of NASH and other chronic liver complications, although this association is less well researched within the region[82-85]. The scarcity of evidence from sub-Saharan Africa means that the true burden and natural history of NAFLD among PLHIV may be underappreciated. This could have negative implications for the development of evidence-based public health interventions tailored to the sub-Saharan African context.

Table 2 Prevalence of metabolic syndrome among people living with human immunodeficiency virus in sub-Saharan Africa from selected studies

Ref.	Country	Study design	Sample size, *n*	MetS diagnostic criteria	Prevalence of MetS	Independent risk factors[1]
Adébayo *et al*[53]	Benin	Cross-sectional	244	IDF	18.4%	-
Ayodele *et al*[54]	Nigeria	Cross-sectional	291	NCEP/ATP III; IDF; JIS	12.7%; 17.2%; 21.0%	-
Berhane *et al*[55]	Ethiopia	Cross-sectional	313	NCEP/ATP III	21.1%	HAART > 12 mo, female sex
Bosho *et al*[56]	Ethiopia	Cross-sectional	286	NCEP/ATP III; IDF; JIS	23.5%; 20.5%; 27.6%	BMI ≥ 25 kg/m^2, formal education
Dimodi *et al*[57]	Cameroon	Cross-sectional	463	IDF; NCEP/ATP III	32.8%; 30.7%	-
Guira *et al*[58]	Burkina Faso	Cross-sectional	300	IDF	18.0%	-
Hirigo *et al*[59]	Ethiopia	Cross-sectional	185	IDF; NCEP/ATP III	24.3%; 17.8%	BMI ≥ 25 kg/m^2, female sex, age > 40 yr
Mbunkah *et al*[60]	Cameroon	Cross-sectional	173	NCEP/ATP III	15.6%	-
Muhammad *et al*[61]	Nigeria	Cross-sectional	200	NCEP/ATP III	15.0%	-
Muyanja *et al*[62]	Uganda	Cross-sectional	250	AHA/NHLBI	58.0%	Female sex, age > 40 yr
Ngatchou *et al*[63]	Cameroon	Cross-sectional	108	AHA/NHLBI	47.0%	-
Nguyen *et al*[64]	South Africa	Cross-sectional	748	JIS; IDF; NCEP/ATP III	28.2%; 26.5%; 24.1%	-
Obirikorang *et al*[65]	Ghana	Cross-sectional	433	NCEP/ATP III; WHO; IDF	48.3%; 24.5%; 42.3%	-
Sobieszczyk *et al*[66]	South Africa	Longitudinal	160	NCEP/ATP III	19.2%	Older age, time post HIV infection, family history of diabetes, human leukocyte antigen B 81:01 allele
Tesfaye *et al*[67]	Ethiopia	Cross-sectional	374	IDF; NCEP/ATP III	25.0%; 16.8%	Female sex, older age, BMI ≥ 25 kg/m^2, total cholesterol ≥ 200 mg/dL

[1]Based on multivariate analysis in the individual studies. AHA/NHLBI: American Heart Association/National Heart, Lung and Blood Institute; BMI: Body mass index; HAART: Highly active antiretroviral therapy; IDF: International Diabetes Federation; JIS: Joint Interim Statement; MetS: Metabolic syndrome; NCEP/ATP III: National Cholesterol Education Program/Adult Treatment Panel III; WHO: World Health Organization.

LIMITED EVIDENCE ON PLAUSIBLE SYNERGISTIC EFFECT BETWEEN METS AND HBV-HIV CO-INFECTION

Given the substantial risk of MetS and NAFLD among those with CHB and PLHIV, it is important to understand if there is a synergistic effect between MetS and HBV-HIV co-infection in the pathogenesis of chronic liver disease. It is well established that HBV-HIV co-infected individuals are at increased risk of chronic liver disease[86,87]. In addition to the widely recognized mechanisms underlying chronic liver disease in HBV-HIV co-infected individuals, it has now been shown that interactions between HIV gp120 and tat proteins with epithelial cells may induce epithelial-mesenchymal transition, leading to the development of fibrosis[88]. Thus, among those with HBV-HIV co-infection, HIV interactions with liver cells may synergize the development of fibrosis and cirrhosis. In comparison, very little is known of the effect of underlying MetS on the progression of chronic liver disease among HBV-HIV co-infected individuals. While a synergistic effect may be plausible, there is insufficient evidence to confirm this as very few studies report on the burden of MetS among HBV-HIV co-infected individuals. In fact, only three studies met the criteria for this review, one of which involved a sub-Saharan African population[89-91]. In this study involving 41891 ART-naïve HIV-infected individuals from Tanzania, Nagu *et al*[89] sought to identify independent risk factors of elevated ALT titers (> 40 IU/L) as a less sensitive but non-invasive predictor of liver injury and increased risk of mortality from liver disease. Multivariate analysis showed that MetS components including hypertriglyceridemia, hyperglycemia and central obesity, as well as immunosuppression due to uncontrolled

HIV infection and HBV co-infection, were significantly associated with higher risk of elevated ALT[88]. However, the cumulative effect of these risk factors on liver function was not investigated as part of this study.

In a study using the more sensitive transient elastography to assess liver fibrosis and determine associated risk factors among German PLHIV on ART, T2DM and central obesity were found to be associated with the presence of significant fibrosis with (n = 23, 18%) or without (n = 343, 10%) HBV co-infection[90]. Finally, when investigating the etiology of liver-related hospital admissions among PLHIV and CHB patients in the United States, Rajbhandari *et al*[91] found a high prevalence of NASH among HIV mono-infected patients (43.6%) and HBV-HIV co-infected patients (26.9%). In addition to this, a three-fold surge in in-hospital mortality was reported among PLHIV with concomitant HBV co-infection and cirrhosis or portal hypertension compared to those without these comorbidities (odds ratio: 3.00, 95%CI: 1.80-5.02)[91]. Taken together, these findings suggest high risk of adverse outcomes among HBV-HIV co-infected individuals with liver disease and some form of metabolic disorder. It will be important to explore these findings in sub-Saharan Africa where the burden of HBV-HIV co-infection is significantly higher.

While there is an obvious need for further research to improve our understanding of the association between HBV-HIV co-infection and MetS, it is still possible to draw some implications for the clinical management of this population. Comprehensive programs targeted at HBV-HIV co-infected individuals that integrate ART programs with routine screening for MetS components and promotion of lifestyle modifications could be low-hanging fruits for effectively reducing the risk of adverse outcomes including chronic liver disease. Where underlying MetS is left undetected and uncontrolled there may be negative implications for ART outcomes. For example, the presence of central obesity and T2DM has been associated with lower rates of fibrosis regression among patients with CHB undergoing long-term treatment with nucleotide/ nucleoside analogues[92]. The effect of nucleotide/nucleoside analogues on MetS components such as lipid abnormalities has also been investigated. A retrospective cohort study that compared tenofovir disoproxil fumarate (or TDF, which forms part of some ART regimens) and entecavir (ETV) therapy among CHB patients found that serum lipoprotein lipid levels significantly differed pre- and post-treatment for median total cholesterol (3.92 *vs* 4.42 mmol/L, $P < 0.01$), LDL-C (2.25 *vs* 2.51 mmol/L, $P < 0.01$) and HDL-C (1.14 *vs* 1.34 mmol/L, $P < 0.01$) in the TDF arm whereas no significant differences were observed in the ETV group[93]. In fact, TDF was shown to be an independent predictor of changes in lipid profiles, with TDF-treated patients being 14.0%, 13.0% and 20.0% more likely to attain a reduction in levels of total cholesterol, LDL-C and HDL-C, respectively, compared to those on ETV. However, triglycerides levels did not change over the follow-up period (median of 56 mo) in the TDF group[93]. Similarly, while a recent phase IV randomized control trial demonstrated the superiority (by 8.0%-10.0%) of pitavastatin over pravastatin in reducing LDL-C among PLHIV with dyslipidemia, there was no difference between either cholesterol-lowering drug in altering triglyceride levels[94].

CONCLUSION

As HBV-HIV co-infected individuals are living longer due to the benefits of ART, there is a need to ensure optimal quality of life, and this can be achieved by reducing the risk of comorbidities like MetS and chronic liver disease. There is a need to expand the research agenda in sub-Saharan Africa in order to improve our understanding of the role of MetS in the progression of chronic liver disease among the substantial population of CHB and HBV-HIV co-infected individuals within the region. Future research should include rigorous longitudinal studies to allow for the determination of the temporal sequence of the development and progression of chronic liver disease among CHB and HBV-HIV co-infected individuals with underlying MetS. In addition, a consensus on ethnicity-specific diagnostic criteria for sub-Saharan African populations is required in order to improve the assessment of MetS within the region.

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MINIREVIEWS

Thymosin alpha 1: A comprehensive review of the literature

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Abstract

Thymosin alpha 1 is a peptide naturally occurring in the thymus that has long been recognized for modifying, enhancing, and restoring immune function. Thymosin alpha 1 has been utilized in the treatment of immunocompromised states and malignancies, as an enhancer of vaccine response, and as a means of curbing morbidity and mortality in sepsis and numerous infections. Studies have postulated that thymosin alpha 1 could help improve the outcome in severely ill corona virus disease 2019 patients by repairing damage caused by overactivation of lymphocytic immunity and how thymosin alpha 1 could prevent the excessive activation of T cells. In this review, we discuss key literature on the background knowledge and current clinical uses of thymosin alpha 1. Considering the known biochemical properties including antibacterial and antiviral properties, time-honored applications, and the new promising findings regarding the use of thymosin, we believe that thymosin alpha 1 deserves further investigation into its antiviral properties and possible repurposing as a treatment against severe acute respiratory syndrome coronavirus-2.

Key Words: Thymosin alpha 1; Thymalfasin; Immunomodulating; T lymphocytes; Infectious diseases; Immune deficiency; Oxidative damage

Core Tip: Thymosin alpha 1 is a naturally occurring peptide in the human thymus, which has long been recognized for its immune-modulating properties. The synthetic

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analog of thymosin alpha 1 has various clinical applications, such as in infectious diseases, malignancies and in immunocompromised states. There is emerging data postulating that this peptide could be of benefit in the treatment of severe acute respiratory syndrome coronavirus-2 infection. We herein discuss the underlying knowledge, current clinical uses and results of recent studies of thymosin alpha 1.

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INTRODUCTION

Thymosin alpha 1 is a 28 amino acid peptide originally isolated from the thymus[1], which has been extensively studied in terms of its functions in the immune system. Thymosin alpha 1 has long been recognized as an immune enhancing, immune modulating, as well as an immune restoring agent[2], and as such it has been utilized in several clinical and research settings. The synthetic form of thymosin alpha 1, thymalfasin, is approved in more than 35 countries for the treatment of hepatitis B and C and as an immune enhancer in several other diseases[1]. More specifically, it has been of benefit as a means of augmenting immune response in immune deficiencies[3], psoriatic arthritis[4], aging[3], as well as in increasing response to vaccines[3] and decreasing chemotherapy-induced toxicity[5]. It has additionally been of value in treating oncologic patients, especially those with hepatocellular carcinoma, renal cell carcinoma and non-small cell lung cancer[5]. Last but not least, it has been used in the fight of numerous infections, such as human immunodeficiency virus (HIV)[6], pseudomonas[1], and mold toxicity[7], as well as sepsis[8], and recently in severely ill coronavirus disease 2019 (COVID-19) patients[9]. In light of the current pandemic situation, efforts are being made worldwide to understand the impact of infection caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) on the immune system in the hopes of getting closer to an effective treatment. To this end, it would be worthwhile to further investigate thymosin alpha 1 through the relevant published literature. In this review, we aim to understand the characteristics of thymosin alpha 1, from its chemical structure and biological properties all the way to its clinical applications, their safety and efficacy which would provide an insight on whether it could be used as a therapeutic option to help curb mortality and improve outcomes in severely ill COVID-19 patients.

BIOCHEMISTRY

Thymosin proteins are short, positively charged, and inherently unregulated peptides. Induction of thymosin protein configuration *via* organic reagents, such as trifluoroethanol, hexafluoroisopropanol, dodecyl trimethylammonium bromide, and Zn^{2+} ions, charges the proteins neutralizing them at a low PH to potentiate their absolute effects[10]. The nuclear magnetic resonance structure of thymosin alpha 1 has been determined by mixing in 40% trifluoroethanol/60% water (v/v) solvent. The study has determined 800 MHz of a polypeptide chain consisting of 28 residues. To comprehend its distinct structure, multiple molecular trials with solvent composed of 40% trifluoroethanol/60% transferable intermolecular potential with 3 points water (v/v) were utilized to create a three-dimensional configuration of the peptide. Ultimately, it was able to depict a distorted helical configuration with two stable regions: Alpha-helix site from 14-26 residues and two double turns in the β region in the N-terminal site consisting of 12 residues[11].

Thymalfasin, the synthetic analog of thymosin alpha 1, induces interleukin (IL)-2 production, differentiation of immature cord blood lymphocytes, production of B cell growth factors, and increased macrophage antigen presentation efficiency. It is used to

treat chemotherapy-induced immunosuppression and to enhance the efficacy of influenza and hepatitis B vaccines in immunocompromised patients[12]. Thymosin alpha 1 therapy modulates and partially normalizes T-lymphocyte numbers and function. T cell rosette percentages have been shown to increase in patients with T cell lymphopenia. Thymalfasin may benefit conditions such as T cell lymphopenia, immunosuppression, and immune dysregulation seen in COVID-19 due to SARS-CoV-2 induced cytokine storm and the immunosuppressive effects of its viral envelope proteins[13]. This may be why Thymalfasin has been used in China for general treatment of COVID-19 patients since April 2020[14].

EXTRACTION AND ANALYSIS

Thymosin alpha 1 is a peptide hormone that is endogenously produced by the thymus gland and potentiates T cell-mediated immune responses *via* differentiation and maturation of T-cell progenitor cells, activation of dendritic and natural killer cells, and stimulation of cytokine-mediated inflammation[15]. Since first isolated from a preparation of bovine thymuses, named the thymosin fraction 5 in 1977, thymosin alpha 1 has been widely recognized for its immune-enhancing properties. Therefore, various efforts have been made towards finding the most efficient method for its production and purification. There are currently three distinct ways bioactive thymosin alpha 1 can be obtained. The first method of extraction is *via* isolation from calf thymuses. It can also be extracted from thymosin fraction 5, which was first isolated from calf thymuses using the technique described in 1975[12]. The second method is through solid-phase synthesis, which is a purely chemical way of peptide synthesis and is nowadays the only method accepted for production of thymosin alpha 1 for clinical use. Lastly, genetic engineering expression makes use of the advances in biotechnology to produce purified recombinant thymosin alpha 1 from either prokaryotic organisms such as *Escherichia coli*, or eukaryotic organisms such as yeast, plants or Pichia Pastoris. Regarding thymosin alpha 1 expression in *Escherichia coli*, numerous expression systems have been developed based on the insertion of the recombinant gene for human thymosin alpha 1 in different vectors, such as pGEX-2T, pThioHis B, pBV222. According to Antachopoulos *et al*[7] (2012), the most promising results came from the BL21/pET-28a system, with thymosin alpha 1 being 70% of total bacterial protein production. The protein can then be analyzed *via* sodium dodecyl sulfate-polyacrylamide gel electrophoresis or by measuring ultraviolet light absorbance at 215 nm. For purification, the primary methods proposed are nickel affinity chromatography, thermal denaturation, and high-performance liquid chromatography. Thymosin alpha 1 expression in yeast is an attractive alternative because post-translational modifications and the development of stable cell lines are made possible[6].

Chen *et al*[16] describe their own yeast-based expression system for thymosin alpha 1, which proved to be effective in producing thymosin alpha 1 capable of increasing CD8+ counts in mice pre-treated with cyclophosphamide. An example of thymosin alpha 1 expression in plants (transgenic tomato Solanum Lycopersicum) is described by Chen *et al*[17]. As promising as it may seem, the genetic engineering method for thymosin alpha 1 production has not yet been introduced into clinical practice, primarily due to difficulties pertaining to extraction and purification. Other than direct extraction from calf thymus, which can only produce trace amounts of the peptide, thymosin alpha 1 used for therapeutic purposes comes from chemical synthesis.

Enzyme-linked immunosorbent assay and radioimmunoassay are the most commonly used methods for quantitative analysis of the peptide. Tuthill *et al*[18] also suggest liquid chromatography with tandem mass spectrometry, which has proven to be accurate, precise, and sensitive for measurement of thymosin alpha 1 in the serum[18].

STORAGE OF THYMOSIN ALPHA 1

Thymosin alpha 1 should be stored at -20 degrees Celsius. Lyophilized thymosin alpha 1 may remain stable for up to three weeks at room temperature; however, for long term storage, it should be kept below -180 degrees Celsius and stored in the desiccated form. When ready to use, it may be reconstituted and subsequently stored at 40 degrees Celsius for a period of two to seven days. If the intention is to store thymosin alpha 1 for a longer period of time, then it is advised to store it in combination with a

carrier protein such as 0.1% human serum albumin or bovine serum albumin. It is recommended to avoid repeated freezing and thawing[19].

BIOLOGICAL ACTIVITIES AND HEALTH BENEFITS

Thymosin alpha 1 functions as a toll-like receptor (TLR)-9 and TLR-2 agonist in both myeloid and dendritic cells, the professional antigen-presenting cells[20]. By targeting TLRs, thymosin alpha 1 can stimulate the adaptive immune response, which is essential for fighting viral, bacterial, and fungal infections and cancers, as well as stimulation of posterior humoral immunity[20-22]. Additionally, thymosin alpha 1 can increase levels of IL-2, IL-10, IL-12, interferon (IFN)-α, and IFN-γ[23]. The role of thymosin alpha 1 in stimulating T-cell dependent antibody production is also the reason why it has been considered as a vaccine adjuvant for enhancing response to vaccines[24].

Thymosin alpha 1 has a wide range of biological activities that range from anti-tumor to immune-modulating properties (Figure 1). The immune response of thymosin alpha 1 is due to its action in elevating the activity of T cell maturation into CD4+/CD8+ T cells. It works to directly activate natural killer cells as well as CD8+ T cells through which it kills virally infected cells. Thymosin alpha 1 has a negative effect on IL-1β and tumor necrosis factor-α, which in turn leads to a decreased inflammatory response and is quite beneficial in conditions such as chronic hepatitis and acute pancreatitis. Not only does it play a role in enhancing cytokine expression, but it also increases the prominence of major histocompatibility complex I/viral antigens on their respective target infected cells and decreases viral replication[6]. Naylor and his associates pointed out that thymosin alpha 1 does not only have one but rather a varied range of targets for its immune-enhancing activity[25].

Thymosin alpha 1 has exhibited the ability to restrain tumor growth, hence its use in the treatment of various cancers. It has anti-proliferative properties which have been exhibited in lung and liver tumor metastases. According to studies conducted by Moody *et al*[25], the anti-tumor activity of thymosin alpha 1 worked best with small tumor size. Overall, thymosin alpha 1 works *via* two main mechanisms: Either stimulating the immune system or employing its anti-proliferative activities on tumor cells. The protective action of thymosin alpha 1 against oxidative damage as a result of its effect on liver superoxide dismutase and glutathione peroxidase has been explored by Armutcu *et al*[26].

Since thymosin alpha 1 is a polypeptide naturally present in the thymus, it plays a fundamental role in the control of inflammation, immunity, and tolerance. Thymosin alpha 1 has an immune-modulating action through its interaction with toll-like receptors. Due to the action of thymosin alpha 1 on other cell types, it is used as a therapeutic agent for diseases with evident immune dysfunction[4]. Clinical trials with thymosin alpha 1 for diseases like DiGeorge syndrome, non-small cell lung cancer, hepatocellular carcinoma, hepatitis B and C, HIV, and melanoma have been conducted and yielded promising results[27,28]. FDA approved the orphan drug thymalfasin (Zadaxin) for treatment of malignant melanoma, chronic active hepatitis B, DiGeorge anomaly with immune defects, and hepatocellular carcinoma due to its immunomodulatory and anti-tumor effect.

CLINICAL AND COMMERCIAL APPLICATIONS

Thymosin alpha 1 has been extensively tested and its synthetic form, thymalfasin, is widely used in the clinical field (Figure 2). Some of its applications are as follows.

Hepatitis B

The safety and efficacy of thymosin alpha 1 in patients with chronic hepatitis B have been tested through clinical trials. Thymosin alpha 1 has been tested as monotherapy as well as in combination with interferon-alpha and other nucleoside analogs. There has been found a complete virological response rate [clearance of serum hepatitis B virus deoxyribonucleic acid and hepatitis B e antigen] of 40.6% in patients given 1.6 mg subcutaneous injection twice a week and 26.5% in patients given the same regimen for 52 wk[29]. However, it is important to note that treatment of Hepatitis B using thymosin alpha 1 was only used in the era of interferon and is now obsolete in the era post-discovery of direct antiviral agents.

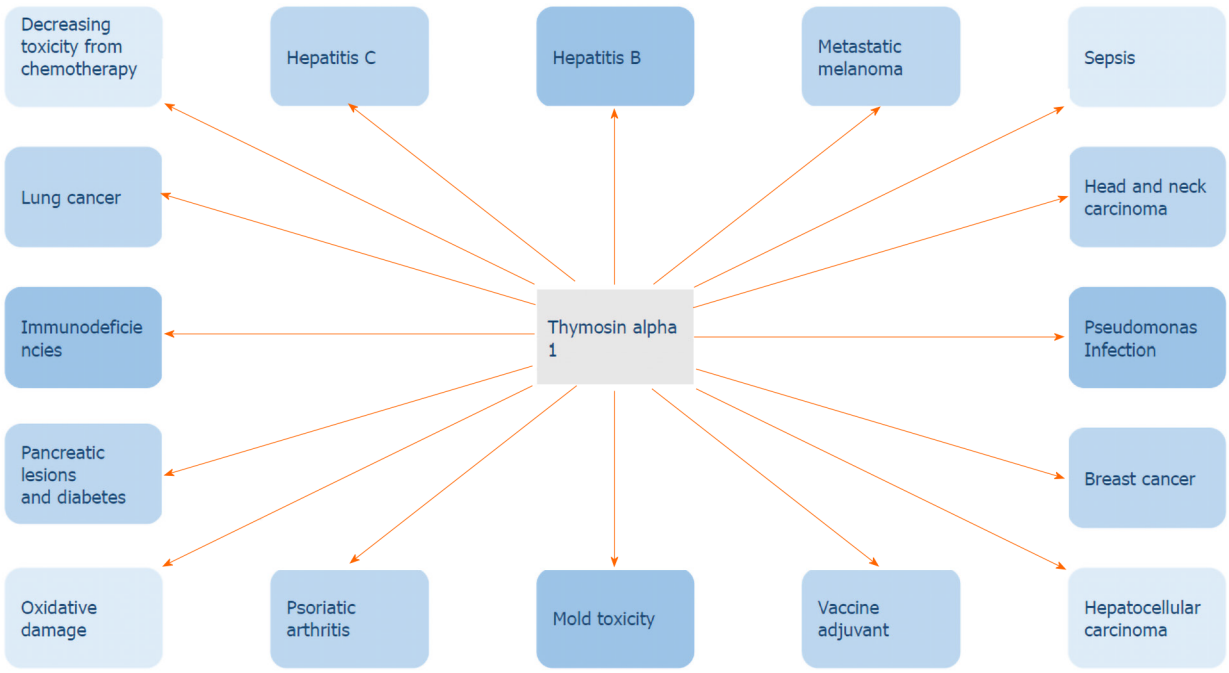

Figure 1 Thymosin alpha 1 has a wide range of biological activities. IL: Interleukin; IFN: Interferon; TLR: Toll-like receptors.

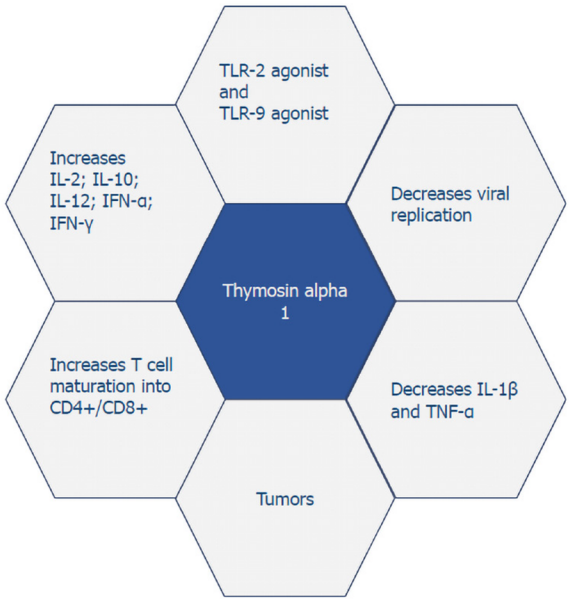

Figure 2 Clinical applications of thymosin alpha 1.

Hepatitis C

Thymosin alpha 1 as a monotherapy does not seem to be useful in treating hepatitis C infection. However, combination therapy of thymosin alpha 1 and pegylated interferon alpha 2a could effectively repress viral replication in hepatitis C patients. Thymosin alpha 1, in combination with interferon-alpha 1 has also been tested for treatment in patients with chronic hepatitis C. Moreover, thymosin alpha 1 is well tolerated, with no significant adverse effects observed. A meta-analysis conducted by Sherman, included many trials showing the superiority of the combination of thymosin alpha 1 and interferon alpha 1 compared to interferon alpha mono-therapy[30]. It remains important to note that similar to Hepatitis B, the treatment of Hepatitis C with thymosin alpha 1 has been discontinued in favor of direct antiviral agents.

Sepsis

The use of thymosin alpha 1 in patients with sepsis has shown a significant decrease in mortality due to multiple-organ failure, which is the primary cause of death in sepsis[8].

HIV infection

Thymosin alpha 1, interferon alpha 1, and zidovudine combination therapy has been well-tolerated in HIV patients. Thymosin alpha 1 enhances the function and increases the number of CD4+ T cells, while it also decreases viral load. Thymosin alpha 1 influences thymic T-cell output. The safety and efficacy of thymosin alpha 1 in combination with highly-active antiretroviral therapy in stimulating immune reconstitution has been proven[6]. It has been shown that thymosin alpha 1 is well tolerated, and could dramatically increase the levels of signal joint T cell receptor excision circles in patients with advanced HIV disease. Prolonged use of high-dose thymosin alpha 1 is more effective[2].

Pseudomonas - bone marrow transplant patients

Thymosin alpha 1 is also used in other infections like pseudomonas or infections following bone marrow transplant[1].

Mold toxicity

This thymic peptide has the ability to prime dendritic cells and to enhance Th1 and Treg cells so that inflammation is balanced, and an antifungal response is generated. Th1 response will activate the production of Th2 cytokines (IFN-γ, IL-2, IL-12, IL-18), stimulating phagocytic activity. Therefore, cytotoxic CD4+, CD8+, and T cells and opsonizing antibodies will be produced, generating a protective effect against fungal pathogens[7].

Immune deficiency

Treatment with thymosin alpha 1 serves as a stimulus for IL-2 receptor expression and IL-2 internalization. It also has a restoring effect on patients with a suppressed lymphokine-activated killer cell activity and with immunodeficiency[29]. Acting through Toll-like receptors in both myeloid and plasmacytoid dendritic cells, thymosin alpha 1 stimulates the signaling pathways and initiates the production of immune-related cytokines. Thus, thymosin alpha 1 is anticipated to bring about encouraging results in the treatment of immunocompromised patients. Overall, it improves immune system function without causing adverse events[13].

Psoriatic arthritis

Thymosin alpha 1 is a potent modulator of immunity and inflammation. Evidence is growing that diseases characterized by deregulation of the immune system and inflammation, such as psoriatic arthritis, are associated with serum levels of thymosin alpha 1 significantly lower than those of healthy individuals. The data is consistent with the role of thymosin alpha 1 as a regulator of immunity, tolerance and inflammation in patients with psoriatic arthritis[4].

Vaccine adjuvant

The use of thymosin alpha 1 as an adjuvant to the influenza vaccine has shown promising results, especially among elderly and immunocompromised patients[31]. Thymosin alpha 1 has also been shown to improve the immunogenicity of the influenza vaccine[3].

Decreasing toxicity from chemotherapy

Clinical studies show that thymosin alpha 1 has been utilized in patients with different malignancies, reducing the toxicity of chemotherapy, and improving the quality of life. An increase in the numbers and functions of immune cells and the decrease of toxicity from chemotherapy was also an effect of utilizing this medication. In general, fewer infections occurred during chemotherapy, neurotoxicity decreased, and the quality of life improved[5].

Oxidative damage, pancreatic lesions and diabetes

Many studies have shown that thymosin alpha 1 has protective effects against oxidative damage. By remarkably amplifying the activity of catalase, superoxide dismutase, and glutathione peroxidase, thymosin alpha 1 reduces the production of reactive oxygen species and prevents oxidative damage to hepatic tissue. Thymosin

alpha 1 has well-established antiproliferative properties seen with various human malignancies and this is a result of its capacity to decrease oxidative stress[6]. It also helps ameliorate pancreatic damage and the resulting diabetes by reducing the production of malondialdehyde and by improving the function of superoxide dismutase and catalase. The antioxidant properties of thymosin alpha 1 are considered to be of great benefit in the treatment of pancreatic lesions[32].

Applications in oncologic patients

Multiple studies have shown promising results for the use of thymosin alpha 1 in patients with metastatic melanoma, head and neck carcinoma, lung cancer, breast cancer, and hepatocellular carcinoma[33]. Thymosin alpha 1 is indicated as adjuvant for chemotherapy-induced immune depression, immune insufficiency, and immune suppression in patients[5]. In addition, it has been shown that thymosin alpha 1 in combination with chemotherapy or radiation improves survival rate in patients with non-small cell lung cancer, which accounts for 85% of all lung cancers and is known for its low responsiveness to chemotherapy[5].

SAFETY AND DOSES

Thymosin alpha 1 is usually found in an injection form and is commonly prescribed by a primary care physician. Thymosin alpha 1 is usually administered twice a week *via* a subcutaneous route. The standard single dosage ranges from 0.8 to 6.4 mg, while multiple doses range from 1.6 to 16 mg for five to seven days. Utilized in various illnesses such as liver disease, cancer, and autoimmune diseases, thymosin alpha 1 has been shown to be well-tolerated and safe[34].

ADVERSE EFFECTS AND CONTRAINDICATIONS

Thymalfasin, the synthetic form of thymosin alpha 1, is usually well tolerated. The most common adverse effects include local irritation, redness, or discomfort at the site of injection. In clinical trials, the combination of thymalfasin with interferon 2b was reported to have rare side effects such as fever, fatigue, muscle aches, nausea, vomiting, and neutropenia when compared to interferon-alpha 2b alone or with placebo[34]. Thymalfasin is contraindicated in patients with hypersensitivity to thymosin alpha 1 or any of the components of the injection. Due to the immunomodulatory action of thymalfasin, it is also contraindicated in immunosuppressed patients, such as organ transplant recipients, unless the benefits of the treatment exceed the risks[35].

EVIDENCE FROM PREVIOUS HUMAN CLINICAL STUDIES

Thymosin alpha 1 has been utilized in various cases to enhance cell-mediated immunity and for the treatment of a multitude of different diseases (Table 1). A study was performed to demonstrate the effect of thymosin alpha 1 in the human breast cancer lines ZR-75-1, MCF-7, MDA-MB-231, MCF-10A and BT-549. For this experiment, thymosin alpha 1 was dissolved in sterile water and stored in 2 mL plastic tubes at -20 °C. Results showed that thymosin alpha 1 inhibited cell proliferation and induced apoptosis in human leukemia, non-small cell lung cancer, melanoma, and other cancers. Apoptosis was significantly induced in human breast cancer and leukemia cell lines with a thymosin alpha 1 concentration of 100 to 160 IM. Additionally, data exhibited that ZR-75-1 and MCF-7 cells display different sensitivities to thymosin alpha 1. In general, the study revealed that thymosin alpha 1 could be a possible approach to breast cancer treatment[36]. Other studies demonstrate that thymosin alpha 1 could be a promising therapy for severe sepsis. Various small-scale studies as well as a large-scale, multicenter, single-blinded, and randomized control trial were conducted in six tertiary teaching hospitals in China, with the purpose of demonstrating the vital role thymosin alpha 1 plays in sepsis therapy. Patients admitted to the intensive care unit with severe sepsis were distributed randomly among the control group and the thymosin alpha 1 group. Hypodermic injections of 1.6 mg of thymosin alpha-1 or normal saline were distributed to all individuals two times a day for five days; afterwards, the dose was reduced to once

Table 1 Summarizing pre-clinical and clinical studies

Pre-clinical studies		
Ref.	**Year**	**Application of thymosin alpha 1**
Guo *et al*[36]	2015	The anti-tumor effect of thymosin alpha 1 was studied on human cancer cell lines. The study concluded that thymosin alpha 1 can decrease proliferation and induce apoptosis in human leukemia, non-small cell lung cancer, melanoma, and other cancers. The study concluded that thymosin alpha 1 could be an approach to breast cancer treatment
Clinical studies		
Sherman *et al*[29]	2010	Thymosin alpha 1 was tested as monotherapy and in combination with interferon-alpha for the treatment of chronic hepatitis B. It was also shown to stimulate IL-2 receptor expression and IL-2 internalization and to enhance immune response in patients with immunodeficiency
Eckert *et al*[30]	1994	Combination therapy of thymosin alpha 1 and pegylated interferon alpha 2a preferred over interferon monotherapy for the treatment of chronic hepatitis C
Li *et al*[8]	2015	Significant decrease in mortality due to multiple organ failure in patients with sepsis
Li *et al*[6]	2010	Thymosin alpha 1 can be safely used as an adjuvant to antiretroviral therapy in HIV patients. It helps increase CD4+ count, stimulates the function of CD4+ cells, and helps decrease viral load. By amplifying the activity of catalase, superoxide dismutase, and glutathione peroxidase, it decreases oxidative damage to tissues. Thymosin alpha 1 reduces tumor cell proliferation in human malignancies by decreasing oxidative stress
Matteucci *et al*[2]	2017	Thymosin alpha 1 significantly increases levels of sjTREC in patients with advanced HIV disease
Camerini *et al*[1]	2015	Thymosin alpha 1 can be used in pseudomonas infections or infections following bone marrow transplant
Antachopoulos *et al*[7]	2012	Thymosin alpha 1 might be effective against mold toxicity
King *et al*[13]	2016	Thymosin alpha 1 increases cytokine production and is expected to be beneficial in immunocompromised patients
Pica *et al*[4]	2018	It has been postulated that thymosin alpha 1 can help regulate immunity and reduce inflammation in patients with psoriatic arthritis
Panatto *et al*[31]	2011	Thymosin alpha 1 has shown promising results as an adjuvant to the influenza vaccine
Carraro *et al*[3]	2012	Thymosin alpha 1 improves immunogenicity of the influenza vaccine
Qin *et al*[32]	2009	Thymosin alpha 1 can reduce oxidative damage to the pancreas and mitigate the risk of resulting diabetes
Costantini *et al*[33]	2019	Thymosin alpha 1 has shown promising results in patients with malignancies, such as metastatic melanoma, head and neck carcinoma, lung cancer, breast cancer, and hepatocellular carcinoma
Romani *et al*[21]	2007	A single-blind randomized control trial was conducted in six tertiary hospitals in China to study the beneficial effects of thymosin alpha 1 on patients with sepsis. The results showed 9% lower mortality in the treatment group compared to the control group
Sugahara *et al*[37]	2002	Patients with chronic hepatitis B who were treated with thymosin alpha 1 showed an overall improvement in serum ALT levels. ALT levels were reduced to normal in 42.9%. A total disappearance of serum HBV DNA was noted in 28.6% of patients

IL: Interleukin; sjTREC: Signal joint T cell receptor excision circles; HIV: Human immunodeficiency virus; ALT: Glutamic-pyruvic transaminase; HBV: Hepatitis B virus; DNA: Deoxyribonucleic acid.

per day. Results showed that the thymosin alpha 1 group was 9.0% lower in mortality rate than the control group[21].

As discussed above, one of the strongest properties of thymosin alpha 1 is its role in the activation of T cell responses in the body. A study in seven patients with chronic hepatitis caused by hepatitis B virus tried to identify the immunomodulatory properties of thymosin alpha 1. Each individual was treated for a total of 24 wk with a hypodermic injection at a dose of 1.29/0.4 mg/body/day six times weekly for the first 2 wk and then twice weekly for an additional 22 wk. Subsequently, liver biopsies were performed to gather data. The serum alanine transaminase levels improved to 47.39/17.0 IU/L and normalized in 42.9% of patients after 48 wk of treatment. However, complete disappearance of serum hepatitis B virus deoxyribonucleic acid was seen in 28.6%. Thymosin alpha 1 also affected maturation of T-cells, demonstrating its high immunomodulatory properties. Overall, it has been reported that combination therapy with thymosin alpha 1 and IFN-α has demonstrable biological activity in patients with viral hepatitis[37].

THYMOSIN ALPHA 1/THYMALFASIN *VS* THYMOSIN BETA 4/TIMBETASIN

Thymosin alpha 1 and thymosin beta 4 are two hormone peptides that are secreted from the thymus and have vastly different chemical compositions and immunological actions. These proteins are separated from thymosin fraction 5 and have the potential to change a variety of immune functions in mammals. Thymosin alpha 1 is thought to be responsible for rebuilding the immune system by enhancing cell-mediated immunity in animals without a thymus gland. Thymosin beta 4 is in the family of actin monomer-sequestering proteins which essentially regulate unpolymerized actin and have an active role in maintaining the free G-actin monomers in the cytoplasm. Thymosin alpha 1 is clinically relevant in various types of cancer, specifically hepatocellular carcinoma, lung cancer and melanomas. Thymosin beta 4, has a strong response to virally infected cells. It is currently being tested as a possible therapy against influenza, HIV, and acquired immune deficiency syndrome[38-41].

COULD THYMOSIN ALPHA 1 IMPROVE THE OUTCOMES IN COVID-19 PATIENTS?

The COVID-19 pandemic has had a worldwide impact and multiple studies have shown the immunological effects of this disease. All countries affected by SARS-CoV-2 are focused on searching for an effective treatment. Thymosin alpha 1 has a very prominent role in both immunity control and inflammation (Table 2). So far, it has been used in various pathologic conditions: Infections, sepsis, immune deficiencies and malignancies, just to name a few. It has also been found to curb mortality in several of them, such as sepsis and HIV infection. Although clinical studies on the efficiency of thymosin alpha 1 in treating COVID-19 are still limited, it would be of great value to further explore the potential benefits that this drug can bring about in mitigating the devastating effects of the current pandemic.

A recent study in COVID-19 patients demonstrated how thymosin alpha 1 significantly promoted the proliferation of activated T cells and this led to a critical prevention of lymphopenia in infected patients. In total, there were 25 severely and critically ill patients who participated in the study. Eleven of them received daily treatment of thymosin alpha 1 for one week, while the rest of the patients remained untreated. Data illustrates that patients in the thymosin alpha 1 treatment group had a higher number of lymphocytes than patients without treatment[42]. In another retrospective study conducted in China, patients in the treatment group received subcutaneous injections of 10 mg thymosin alpha 1 once per day for at least seven consecutive days. Thymosin alpha 1 supplementation showed improvement and restoration of T cell counts in COVID-19 patients with severe lymphocytopenia and, in the end, thymosin alpha 1 supplementation reduced mortality in patients severely ill with COVID-19[30].

In COVID-19 treatment, it has been postulated to administer thymosin alpha 1 as an intramuscular injection for 7 d for patients who have CD8 cells less than 400/μL and CD4 cells less than 650/μL. This is postulated on the understanding that thymosin alpha 1 induction showed improvement in T cell number in elderly patients with comorbidities like hypertension and cardiovascular diseases. Healthy people who are older than 60 years of age should receive thymosin alpha 1 as a supplement to prevent COVID-19 infection[43]. It has also been suggested that thymosin alpha 1 taken before administration of methylprednisolone in COVID-19 patients may prevent steroid-induced death of thymocytes[44]. The National Health Commission of China included thymosin alpha 1 as an alternative treatment option for patients with lymphocytopenia or immunodeficiency.

Currently, there are various ongoing clinical trials registered on clinicaltrials.gov of thymosin in COVID-19 patients (Table 2).

CONCLUSION

Thymosin alpha 1 is a thymus peptide with recognized immune modulating capacity and biochemical properties. The synthetic analogue of thymosin alpha 1, thymalfasin, induces IL-2 and B cell growth factor production, differentiation of immature cord blood lymphocytes, raises efficiency of macrophage antigen presentation, and the modulation and partial normalization of function and number of T-lymphocytes. The

Table 2 Summary of ongoing clinical trials of thymosin and coronavirus disease 2019

Clinical trial number	Location	Status	Condition	Intervention	Results
NCT04428008	United States	Not yet recruiting	COVID-19	Drug: Thymalfasin	Not yet available
NCT04487444	United States	Recruiting	COVID-19	Drug: Thymalfasin	Not yet available
NCT04268537	China	Not yet recruiting	COVID-19	Drug: PD-1 blocking antibody + standard treatment; Drug: Thymosin + Standard treatment; Other: Standard treatment	Not yet available
NCT04320238	China	Recruiting	COVID-19	Drug: Recombinant human interferon Alpha-1b; Drug: Thymosin alpha 1	Not yet available

Data retrieved from clinicaltrials.gov on October 5th, 2020. COVID-19: Coronavirus disease 2019.

effects of immune stimulation occur through TLR action in both the myeloid and plasmacytoid dendritic cells with production of cytokines. The immunosuppressive effects of the SARS-CoV-2 viral envelope in inducing cytokine storm may be modulated with thymosin alpha 1 therapy. This would be especially beneficial in preventing catastrophic events such as cytokine storm in more severe cases. Thymosin alpha 1 and its synthetic analogue thymalfasin have well-studied safety profiles and are well-tolerated with only minor side effects. Clinical studies have demonstrated the significant role of thymosin alpha 1 in immune and inflammatory responses, and extensive research has shown its effective use in a myriad of diseases ranging from hepatitis and HIV to immune deficiencies and cancers, as well as its use as a vaccine adjuvant.

Within the context of COVID-19 infection, it has been shown to reduce mortality in those with severe disease and aid in restoring some immune function through increasing thymic activity. Further study would be highly beneficial in determining if thymosin alpha 1 could serve as a therapeutic agent or in combination with other treatments to mitigate the progression and severity of the disease. For this purpose, we can conclude that further studies are mandated for using thymosin alpha 1 in these patients.

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SYSTEMATIC REVIEWS

Reinfection risk of novel coronavirus (COVID-19): A systematic review of current evidence

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Abstract

BACKGROUND

There is recently a concern regarding the reinfection and reactivation of previously reCoVered coronavirus disease 2019 (CoVID-19) patients.

AIM

To summarize the recent findings and reports of CoVID-19 reinfection in patients previously reCoVered from the disease.

METHODS

This study was a systematic review of current evidence conducted in August 2020. The authors studied the probable reinfection risk of novel coronavirus (CoVID-19). We performed a systematic search using the keywords in online databases. The investigation adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist to ensure the reliability and validity of this study and results.

RESULTS

We reviewed 31 studies. Eight studies described reCoVered patients with reinfection. Only one study reported reinfected patients who died. In 26 studies, there was no information about the status of the patients. Several studies indicated that reinfection is not probable and that post-infection immunity is at least temporary and short.

CONCLUSION

Based on our review, we concluded that a positive polymerase chain reaction retest could be due to several reasons and should not always be considered as reinfection or reactivation of the disease. Most relevant studies in positive retest patients have shown relative and probably temporary immunity after the reCoVery of the disease.

Key Words: Reactivation; Reinfection; Postinfection; Coronavirus; CoVID-19; SARS-CoV-2

Core Tip: The reinfection in patients reCoVered from coronavirus disease 2019 (CoVID-19) could create a serious challenge in tackling the CoVID-19 pandemic as the reCoVered patients could be a source of virus spread in society. Previous studies have found a positive viral ribonucleic acid test in some of the discharged CoVID-19 patients 10 to 27 d after reCoVery. Recurrence of CoVID-19 after reCoVery should be differentiated from secondary medical conditions such as super infection, pulmonary embolism, or persistent ribonucleic acid virus that can be disCoVered in respiratory specimens in clinically cured CoVID-19 patients. This review aims to assist a systematic compilation of severe acute respiratory syndrome coronavirus 2 reactivation in reCoVered CoVID-19 patients.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new strain of coronavirus, causes coronavirus disease 2019 (CoVID-19), which was first reported in

China in late 2019 and then spread rapidly worldwide[1-5]. The symptoms of CoVID-19 are high temperature, dry cough, shortness of breath, headache, tiredness, loss of taste or smell, and gastrointestinal symptoms such as diarrhea, anorexia, nausea, and abdominal pain[6-8]. Increased liver enzyme and low counts of lymphocytes (lymphocytopenia) along with increased C-reactive protein (CRP) levels are often present in CoVD-19 patients[9]. It could eventually lead to acute respiratory distress syndrome (ARDS) and death[1,10,11]. Although there is currently no certainty in virus biological behavior and risk of recurrence in the human body, recent studies reported evidence of the virus reactivation following an asymptomatic CoVID-19 infection in a small group of patients[1,12,13].

The risk factors of SARS-CoV-2 reactivation are related to the type of immunosuppressive therapies, factors in the host such as older age, gender, underlying diseases such as diabetes, heart disease, obesity, cancer, and virologic factors[1,14]. Some viruses such as varicella-zoster can remain dormant in host cells for some time, not causing any illness and then reactivate and cause the disease. Recent evidence indicates that SARS-CoV-2 could present similar behavior and reactivate in patients with previously confirmed CoVID-19 infection and cause illness and person-to-person transmission[15].

Recent studies reported that some reCoVered CoVID-19 patients tested positive for virus nucleic acid again[16,17]. Elderly people with comorbidities are more likely to present with CoVID-19 reinfection[18]. Studies suggested that there are three major mechanisms for the reinfection of CoVID-19, including short-lived, ineffective, and strain-specific immune response[19,20].

The gold standard test for diagnosing SARS-CoV-2 infection is nasopharyngeal swab. Swabs from patients who reCoVered from CoVID-19 infection are negative, indicating full reCoVery from CoVID-19 infection. However, a certain number of individuals could be a false negative[17,18], because the samples for identifying SARS-CoV-2 viral load depend on the result of reverse transcription polymerase chain reaction (RT-PCR). SARS-CoV-2 uses angiotensin-converting enzyme-2 (ACE-2) as the receptor for cellular entry. The expression of ACE2 protein in the lungs is more than that in the upper respiratory tract. Therefore, it is important from which site the sample was taken in a patient with CoVID-19, as it may cause false-negative RT-PCR results[21].

In recent studies, SARS-CoV-2 was detected in fecal and sputum specimens of patients who were discharged from the hospital with a negative pharyngeal swab after a couple of weeks[17,22]. In other coronavirus pandemics such as Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), immunoglobulin levels in patients lasted for a minimum of 2 years, indicating that patients could be vulnerable to reinfection after 3 years[23,24]. The tests that detect SARS-CoV-2 genetic material are very sensitive; however, in patients who have reCoVered from CoVID-19, virus fragments can persist in the body and can be detected by the test. This should not be considered as a new infection[23].

The reinfection in patients reCoVered from CoVID-19 could create a serious challenge in tackling the CoVID-19 pandemic as the reCoVered patients could be a source of virus spread in society[19]. Previous studies have found a positive viral ribonucleic acid (RNA) test in some discharged CoVID-19 patients 10 to 27 d after reCoVery[1,19]. Recurrence of CoVID-19 after reCoVery should be differentiated from secondary medical conditions such as super infection, pulmonary embolism, or persistent RNA virus that can be disCoVered in respiratory specimens in clinically cured CoVID-19 patients[25]. This review aims to provide a systematic compilation of SARS-CoV-2 reactivation in reCoVered CoVID-19 patients.

MATERIALS AND METHODS

This study was a systematic literature review of current evidence conducted in August 2020. The authors studied the probable reinfection risk of novel coronavirus (CoVID-19). Our study adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist to ensure the reliability and validity of this study and results.

Data sources

By application of a systematic search and using the keywords in the online databases including PubMed, Scopus, Web of Science, and Science Direct, we extracted all the relevant papers and reports published in English from December 2019 through August

2020. We included several combinations of keywords in the following orders to conduct the search strategy: (1) "Coronavirus" or "CoVID-19" or "SARS-CoV-2" or "Novel Coronavirus" or "2019-nCoV" [Title/Abstract]; (2) "Reactivation" or "Reinfection" or "Postinfection" [Title/Abstract]; and (1) and (2).

Study selection

Three independent investigators retrieved the studies that were the most relevant by titles and abstracts. Subsequently, the full text of the retrieved papers was reviewed and the most relevant papers were chosen according to the eligibility criteria. Then, we extracted the relevant data and organized them in Tables. The original papers that were peer-reviewed and published in English and fulfilled the eligibility criteria were included in the final report.

We considered the exclusion criteria for this study as follows: (1) Papers conveying non-human studies including *in vitro* observations or articles focusing on animal experiments, or discussing CoVID-19 as a whole subject, without citation of the keywords of this study; (2) Papers in which their full text were out of access; and (3) Any suspicious and duplicated results in the databases.

Data extraction

After summarizing, we transferred the information of the authors, type of article (*e.g.*, case reports), publication date, country of origin, sample size, age, gender, and clinical symptoms to a data extraction sheet. Two independent investigators collected this information and subsequently organized them in the Tables. Finally, to ensure no duplications or overlap exist in the content, all the selected articles were cross-checked by other authors.

Quality assessment

As aforementioned, we applied the PRISMA checklist to ensure the quality and reliability of selected articles. Two independent researchers evaluated the consistency and quality of the articles and the bias risk. In either case of discrepancy in viewpoints, a third independent researcher resolved the issue. The full text of selected articles was fully read, and the key findings were extracted.

RESULTS

In this study, 981 documents were identified using a systematic search strategy. After a primary review of retrieved articles, 498 duplicates were removed, and the title and abstract of the remaining 483 resources were reviewed. After applying the selection criteria, 552 articles were excluded, and only 31 articles met the inclusion criteria and were included in the final review (Figure 1).

We have reviewed 35 studies. Eight studies described reCoVered patients with reinfection. Only one study reported reinfected patients who died. In 26 studies, there was no information about the status of the patients (Table 1)[2,10,16,17,20,25-28,30-53].

Several studies indicated that reinfection is not probable and that postinfection immunity is at least temporarily and short; however, other studies, particularly from South Korea and China, reported some reinfection cases. South Korea reported that 116 reCoVered cases of CoVID-19 were found to be positive again[16]. Another study from South Korea reported that up to 163 patients who were presumed to have reCoVered from SARS-CoV-2 ended up testing positive again[20]. Several studies from China do not support reinfection[26-29]. There is only one study from China that reported five cases of reactivation[5].

The results of the present study showed that there are many factors that we need to take into account about reinfection. Some cases may have resulted in a false negative at discharge or patients did not completely meet discharge criteria. Although we should not forget that reinfection could be possible, because some studies have shown humoral immunity weakens over time.

DISCUSSION

Due to the widespread expansion of the CoVID-19 epidemic around the world, there are more and more infected cases, and of course, many people have reCoVered from this viral infection. However, there is recently a concern regarding the reinfection in

Table 1 Identified reinfection risk of novel coronavirus

ID	Ref.	Type of study	Country	Study population	Reinfection outcome			
					ReCoVery	Death	Unknown	Other findings
1	Alizargar *et al*[16]	Letter to the editor	South Korea	CoVID-19 patients	No	No	Yes	South Korea reported that 116 reCoVered cases of CoVID-19 were found positive again
2	Gousseff *et al*[25]	Letter to the editor	France	CoVID-19 patients	Yes	Yes	No	Between April 6 and May 14, 2020, 11 patients were identified (sex ratio M/F 1.2, median age 55, range 19-91 yr). The median duration of symptoms was 18 (13-41) d for the first episode and 10 d for the second one for the 7 patients who eventually reCoVered
3	Chaturvedi *et al*[20]	Review	South Korea	CoVID-19 patients	No	No	Yes	Concerning reports released from the Korea Centers for Disease Control and Prevention (KCDC) have noted that up to 163 patients who were presumed to have reCoVered from SARS-CoV-2 infection ended up testing positive with PCR testing yet again
4	Gomez-Mayordomo *et al*[30]	Short communication	Spain	A case study in a patient with relapsing-remitting MS treated with fingolimod	No	No	Yes	This case suggests that discontinuation of fingolimod during CoVID-19 could imply a worsening of SARS-CoV-2 infection. No information about reinfection
5	Hageman *et al*[31]	Editorial	United States	CoVID-19 in children	Yes	No	No	Limited data suggest that reCoVery might confer immunity
6	Hoang *et al*[32]	Letter to the editor	France	Patients reCoVered from CoVID-19	No	No	Yes	Recurrence of SARS-CoV-2 in patients who had reCoVered from CoVID-19 has been described. However, it is possible that recurrences could actually be persistent infections in which the PCR resulted falsely negative at discharge
7	Inamo *et al*[33]	Letter of biomedical and clinical research	Japan	CoVID-19 patients	No	No	Yes	-
8	Islam *et al*[34]	Review article	Bangladesh	CoVID-19 patients	No	No	Yes	There is a possibility of reinfection as the humoral immunity weakens over time
9	Kang *et al*[26]	Commentary	China	CoVID-19 patients	No	No	Yes	ReCoVered patients become retest positive due to false-negative PCR or patients did not completely meet discharge criteria or due to dead viruses
10	Kannan *et al*[35]	Review article	India	Gene study between SARS-CoV-2 and SARS-CoV-1 and batCoV and MERS-CoV	No	No	Yes	Many researchers observed that there is SARS-CoV-2 reinfection in the same treated patients
11	Karimi *et al*[36]	Letter to the editor	Iran	CoVID-19 patients	Yes	No	No	-
12	Kassa *et al*[37]	Analytic article	Botswana	CoVID-19 patients	No	No	Yes	Not related to our topic but it is said "reinfection" by the family of coronavirus is possible
13	Kellam *et al*[38]	Review article	United Kingdom	Patients with coronavirus infection	No	No	Yes	Immediate reinfection is not possible but reinfection of previously mild SARS-CoV-2 cases is a realistic possibility
14	Kirkcaldy *et al*[39]	Viewpoint	United States	CoVID-19 Patients	No	No	Yes	ReCoVery from CoVID-19 might confer immunity against reinfection, at least temporarily

15	Koks *et al*[40]	Commentary	Australia	CoVID-19 patients	No	No	Yes	No information related to our study except "the testing needs to be repeated several times as persons with negative tests could become positive the next day as a result of a new infection or there plication of the virus"
16	Law *et al*[27]	Letter to the editor	China/Hong Kong	Patients reCoVered from CoVID-19	No	No	Yes	There is currently no supporting evidence for CoVID-19 reinfection after reCoVery but retest can be positive due to several reasons
17	Laxminarayan *et al*[41]	Perspective	India	CoVID-19 in children	No	No	Yes	Reinfection is not probable
18	Leslie *et al*[42]	Letter	United States	SARS-CoV-2 patients	No	No	Yes	Patients with past infection with other coronaviruses that cause common cold may have some immunity to SARS-CoV-2
19	Luo *et al*[43]	Case report	China	Woman with CoVID-19	Yes	No	No	-
20	Meca-Lallana *et al*[44]	Correspondence	Spain	CoVID-19 patients with MS	No	No	Yes	-
21	Okhuese *et al*[45]	Statistical	Nigeria	CoVID-19 patients	No	No	Yes	There is no secondary reinfection in reCoVered patients. However, some reports have shown there have been a few rare cases of reinfection
22	Omer *et al*[46]	Viewpoint	United States	CoVID-19 patients in the United States	No	No	Yes	True reinfection is unlikely
23	Ota *et al*[47]	In brief	United States	Rhesus monkeys	No	No	Yes	-
24	Ozdinc *et al*[48]	Statistical	Turkey	Turkish people infected with CoVID-19	No	No	Yes	There is short term immunity
25	Roy *et al*[17]	Review	India	CoVID-19 patients	No	No	Yes	Reinfection with SARS-CoV-2 seems unlikely taking into consideration our knowledge. We must maintain vigilance during the convalescence period and must take into consideration the probability of genetic mutations, as observed, rather than reinfection by the same strain
26	Steinchen *et al*[49]	Case report	Germany	A case of rheumatoid arthritis and CoVID-19 patient	Yes	No	No	A case of rheumatoid arthritis and insufficient compensation is reported under long-term combination therapy with methotrexate and leflunomide. After going through CoVID-19 infection, a new adjustment was made to a tumor necrosis factor (TNF) blocker. No reactivation of the infection has occurred in the short period of time initiated by the initiated bDMARD (biologic disease-modifying antirheumatic drug) therapy after surviving CoVID-19 infection with positive antibody status. Biologic therapy without mandatory medical indication should not be performed to protect against SARS-CoV-2 infection
27	Ueffing *et al*[50]	Review	Germany	CoVID-19 patients	No	No	Yes	Seven human pathogenic coronaviruses have already been detected in humans, most of which can cause respiratory diseases, but occasionally also conjunctivitis and middle ear infections. Four of the previously known coronaviruses (229E, NL63, OC43, and HKU1) typically cause relatively minor symptoms in the context of human infection of the upper respiratory tract. SARS-CoV and the 2012 MERS-CoV lead to severe respiratory diseases and have a significant mortality rate. Experiences with other coronavirus infections (SARS and MERS) indicate that the immunity could persist for several years. Based on animal experiments, already acquired data on other coronavirus types and plausibility, it can be assumed that seroconverted patients have the immunity of limited duration and only a very low risk of reinfection
28	Verhagen *et al*[51]	Research study	England and Wales	CoVID-19 patients	No	No	Yes	Areas face disproportionate risks for CoVID-19 hospitalization pressures due to their socioeconomic differences and the demographic composition of their populations. Our flexible online dashboard allows policymakers and health officials to monitor and evaluate potential health care demand at a granular level as the infection rate and hospital capacity changes throughout the course of this pandemic. This agile knowledge is invaluable to tackle the enormous logistical challenges to re-allocate resources and target susceptible areas for aggressive testing and tracing to mitigate

								transmission
29	Waltuch *et al*[52]	Case reports	United States	Children with CoVID-19 infection	No	No	Yes	Patients presenting with CoVID-19 associated post-infectious cytokine release syndrome appear to present with prolonged fever (5 d or greater) and GI symptoms with or without rash. This syndrome may overlap with features of Kawasaki Disease and Toxic Shock Syndrome. Patients who present with this clinical picture should have frequent vital signs and will require admission due to the potential for rapid deterioration
30	Tao *et al*[28]	Research study	China	CoVID-19 patients	Yes	No	No	These results implied that the positive result is unlikely caused by the reinfection from others or the remained virus. Rather, it may derive from the remained virus transferred from the lower respiratory tract to the throat or nose with coughing. Accordingly, it is suggested that the specimen detection of bronchoalveolar lavage fluid from the lower respiratory tract should be used as the discharge criteria
31	Zhou *et al*[53]	Review	China	CoVID-19 patients	No	No	Yes	Re-fever and positive nucleic acid test after discharge from the hospital might be due to the biological characteristics of 2019-nCoV, and might also be related to the basic disease, clinical status, glucocorticoid use, sampling, processing, and detecting of patients, and some even related to the reinfection or secondary bacterial virus infection

CoVID-19: Coronavirus disease 2019; F: Female; GI: Gastrointestinal; HBV: Hepatitis B virus; M: Male; MERS-CoV: Middle East respiratory syndrome-coronavirus; MS: Multiple sclerosis; PCR: Polymerase chain reaction; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

previously reCoVered SARS-CoV-2 patients. In the present review, we summarized the recent findings and reports of CoVID-19 reinfection in patients previously reCoVered from the disease. This is important to inform the public regarding the possible risk of reinfection to restrain the transmission of SARS-CoV-2 and control the current epidemic[25].

The findings from the current review of existing evidence suggest two possible scenarios for new infection in patients who were previously reCoVered from CoVD-19, including reinfection and reactivation. Studies have shown some cases of symptom recurrence such as fever, malaise, myalgia, and cough after discharge. The positive PCR test confirmed the infection and suggested reinfection. Although this has been attributed to the biological characteristics of CoVID-19 and other factors, such as underlying diseases, clinical status, glucocorticoid use, sample collection, patient detection, follow-up, and even secondary bacterial infection, it could be due to reinfection with CoVID-19[53,54]. Positive follow-up tests may also derive from the remained virus transferred from the lower respiratory tract to the throat and nose with coughing. Therefore, it is suggested that the fluid collected in the bronchoalveolar lavage of the lower respiratory tract should be tested and used as the discharge criteria in SARS-CoV-2 patients[28]. In fact, a retest can be positive due to several reasons; thus, it is difficult to distinguish between reinfection, reactivation, or other causes.

Among the reviewed studies, six studies emphasized short-term immunity following reCoVery[18,19,25,26,33,35]. One study indicated that the antibodies and the immunity could last about 40 d and that there is a possibility of reinfection or reactivation of latent infection after this period. Therefore, reCoVery from CoVID-19 might not confer immunity against reinfection forever[38,39]. Furthermore, previous studies related to other human coronavirus types suggested the possibility of reinfection by other members of the coronavirus family following reCoVery from a

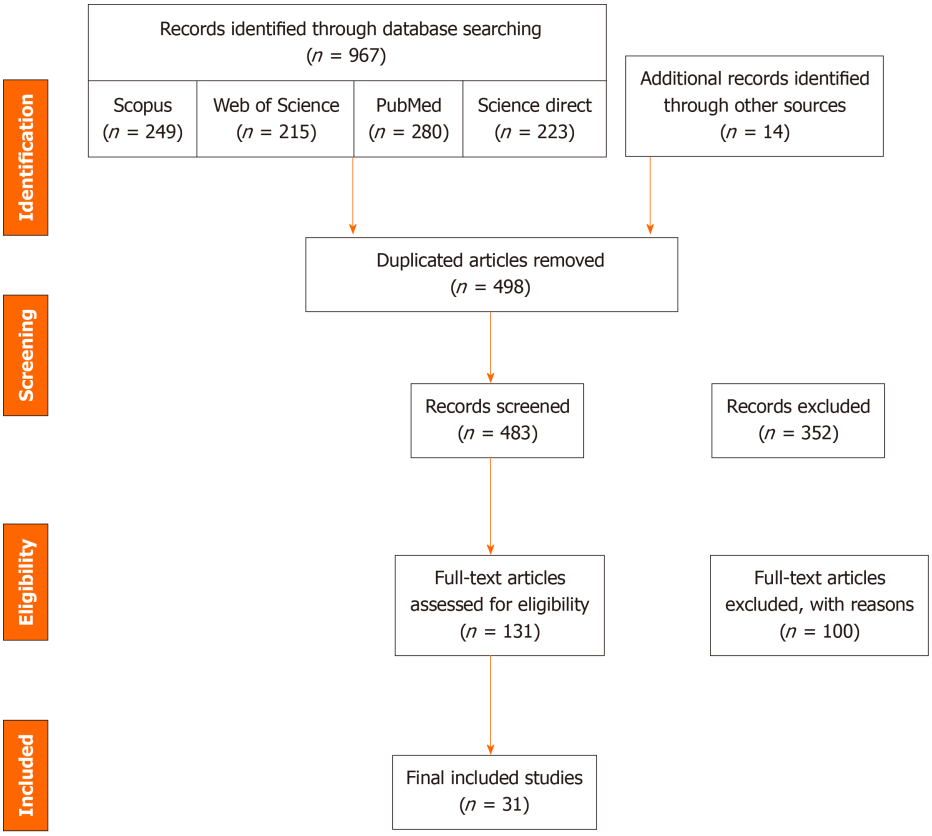

Figure 1 Flow diagram for the selection process of identified articles.

particular type[24]. Although there are previous studies that suggest the reinfection with SARS-CoV-2 is unlikely, we must maintain vigilance during the convalescence period and consider the probability of genetic mutations as observed rather than reinfection by the same strain[6,29,33,34].

The results of the present study showed that there are many factors that we need to take into account about reinfection. Some cases may have resulted in false negative at discharge or patients did not completely meet discharge criteria. We should not forget, however, that reinfection could be possible because some studies have shown humoral immunity weakens over time. The certainty regarding the reinfection in CoVID-19 patients is limited, and we strongly recommend further studies to explore the virological, immunological, and epidemiologic characteristics of SARS-CoV-2 to determine the biological behavior of the virus and describe the potential mechanisms of disease recurrences.

CONCLUSION

In conclusion, positive PCR retest results could be due to several reasons such as the type of specimen collection and technical errors associated with each component of swab testing, the methods used before discharging patients, prolonged viral shedding, and infection by mutated SARS-CoV-2. Thus, it should not always be considered as a reinfection or reactivation of the disease. Furthermore, most relevant studies on symptomatic and positive retest patients have shown relative and probably temporary immunity after the reCoVery of the disease, which means that immunity acquired following primary infection with SARS-CoV-2 may protect from subsequent exposure to the virus at least for a limited period.

ARTICLE HIGHLIGHTS

Research background

Due to the high rate of transmission of coronavirus disease 2019 (CoVID-19), a large number of people around the world became infected with the virus. There is evidence of reinfection with this virus. Therefore, people who get the disease once may be reinfected after reCoVery. Further investigation of reinfection by CoVID-19 is one of the necessities for better management of current conditions.

Research motivation

There have been reports of reCoVered individuals who have a second positive coronary test. This has raised concerns that there is no guarantee that the body will be safe after corona disease, even in the short term.

Research objectives

The aim of the present study was to investigate the available evidence of reinfection in patients with CoVID-19 who have reCoVered.

Research methods

This is a review study of different research types. Since there are myriads of publications released each and every day, with each trying to shed light on this pandemic from different perspectives, we aimed to summarize the very recent and of course the most trustworthy studies regarding the possibility of reinfection of CoVID-19 in this review in order to provide health care professionals and researchers imminent access to a multitude of these studies *via* a concise resource to save their invaluable time for other yet to do tasks.

Research results

The results have shown that there is a slight chance of reinfection. Though the duration of immunity is still unknown and needs to be determined; there is no guarantee that infected patients will not be infected again according to our results. These reinfections can be related to immunity system problems in cases of immunosuppressive disease or drugs that can misdirect our results, but there were many cases that got reinfected without any sign of the problems mentioned above.

Research conclusions

Based on the available evidence, reinfection in improved patients has been proven. Still, there is not enough data to definitely distinguish reinfection, reactivation, or infection with a new mutated severe acute respiratory syndrome coronavirus 2. So, further studies are necessary to understand if a CoVID-19 recurrence is possible and whether it could be considered a real threat.

Research perspectives

We strongly suggest further studies to follow up discharged CoVID-19 patients, check their course of symptoms periodically, and analyze related antibody levels; widespread virological studies are necessary to understand better this new global predicament.

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