Potential Mechanisms of Combined Lead (Pb) and Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Exposure in Liver Disease

Emmanuel Obeng-Gyasi[1]

[1]Affiliation not available

September 19, 2023

Emmanuel Obeng-Gyasi[1]

[1] Department of Built Environment, North Carolina Agricultural & Technical State University; Greensboro, NC, 27411 USA; eobenggyasi@ncat.edu

Abstract: This paper explores the mechanisms of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and lead(Pb) exposure and how they interact to promote liver dysfunction. Coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-2. The environment in which one resides may result in acute and chronically Pb-exposed individuals being infected with SARS-CoV-2. The effects of this exposure on liver dysfunction and its mechanisms are not fully understood. This paper seeks to close this gap in the literature by exploring potential ways this interaction may occur. Results indicated that the interaction of Pb and SARS-CoV-2 and its effects on the liver are likely through the promotion of reactive oxygen species (ROS) production, oxidative stress, and inflammation. Specifically, the rise of inflammation and oxidative stress and the promotion of fibrosis and apoptosis via nuclear factor kappa B (NF-ϰB), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNFα) were all potentially critical pathways identified. The release of liver injury enzymes such as alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) and their role in contributing to thrombosis, coagulopathy, and liver injury are also identified. Finally, how combined exposure may lead to endothelial-mediated inflammation and thrombosis, subsequently bringing forth NASH and NAFLD via increased Plasminogen activator inhibitor-1 (PAI-1) is discussed.

---

*Address correspondence to Emmanuel Obeng-Gyasi, Department of Built Environment; North Carolina Agricultural & Technical State University; Greensboro, NC, 27411 USA; Phone:1-336-285-3132; Fax:1-336-334-7433 Email: eobenggyasi@ncat.edu

KEYWORDS: Lead; Exposure; Mixed Exposures; COVID-19; SARS-CoV-2; Metals; Viruses; Exposome; Hepatic; Liver

1. Introduction

1.1 Background

A new severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) arose in 2019 and triggered an infectious disease known as coronavirus disease 2019 (COVID-19). [1] Coronaviruses are part of the*Coronaviridae*family and*Nidovirales*order. They occur extensively among humans, triggering several ailments that span the "common" flu to death. [2] The virus was initially identified and reported in Wuhan city of China, in December 2019. [3] The SARS-CoV-2 is exceptionally contagious, spread globally in a short

period of time, and was pronounced a global pandemic on March 11, 2020 by the World Health Organization. [4]

Lead (Pb) is a toxicant that persists in the body and environment with a half-life of twenty-eight days in blood and three decades in bone. It was initially added to gasoline due to the belief that it reduced engine knocking and optimized the performance of valves within motors. It was also added to paint because of its moisture-resistant properties. Because of Pb's widespread historical use owing to its physical and chemical properties, numerous populations are acutely and chronically exposed to Pb.

1.2 Transmission

Coronaviruses typically replicate mainly in the epithelial cells of the lower respiratory tract and, to a less significant magnitude, in upper respiratory tract cells. Transmission of SARS-COV-2 mainly occurs from those experiencing symptoms; as such, transmission is likely after an infected individual shows signs of the disease.[5] Individuals with SARS-CoV-2

who are in a very severe state of the disease are more likely to transmit the virus because they release large quantities of infectious particles. [6]

The average quality of recent cases that a case of coronavirus produces over the time of its infectious period (R_0) is between 2–4[7], which indicates that one person can infect between 2 to 4 individuals. [8] Thus, people can be infected rapidly, necessitating monitoring of its distribution and spread.

Pb is mainly stored in bones and teeth and affects organs such as the liver. Regarding Pb exposure, the main exposure routes for Pb are inhalation and ingestion of Pb-infested materials and particles.[9] Inhalation is most common and occurs via fumes that transmit Pb. Absorption of Pb through the skin is unusual. Children are more susceptible to Pb due to their hand-to-mouth activity and the fact that they absorb a more significant percentage of Pb consumed.[10]

The effects of Pb exposure on people vary based on the dose or extent of the exposure. Exposure to elevated levels of Pb in kids has been discovered to diminish attention span and increase petulance and dimness in the brain, bringing forth seizures, headaches, coma, and potentially death. [11]

Despite the mechanisms of Pb toxicity being unclear[12], heme-biosynthesis enzymes and its effects on the antioxidant system have been identified as the key targets of Pb toxicity. In addition, Pb can promote the formation of reactive oxygen species at small blood concentrations Oxidative stress has been identified as the most critical factor in the pathophysiology of Pb poisoning.

The interaction of Pb and SARS-CoV-2 and how it affects hepatic health is a critical question of public health concern. Indeed, the number of adults diagnosed with liver disease in the United States (US) is 4.5 million, representing 1.8% of the population. In addition, 51,642 die from liver disease in the US, which is 15.7 deaths per 100,000 population. [13]

2. Lead and Liver Injury

The liver is the biggest organ in the body and receives extensive circulatory supply from both the hepatic artery and the portal vein. Therefore, the liver comes into contact with Pb and its effects are potentially pronouced. Research on the hepatotoxic consequences of Pb has shown that exposure to Pb possibly modifies xenobiotic and cholesterol metabolism, in addition to inducing hepatic hyperplasia.[14] Oxidative stress is potentially significant in the pathway of the pathophysiology of Pb toxicity. In a study by Hsu and Leon Guo [15], results revealed oxidative stress brought forth by lead exposure contributes to the pathophysiology of Pb toxicity by disrupting the antioxidant/prooxidant equilibrium in cells. In fact, Pb exposure may trigger the production of ROS and alteration of the antioxidant system in exposed individuals and subsequently adversely affects the liver. Pb-exposed patients store a lot of consumed Pb in the liver. [16]

Immune system dysfuction is also potentially a signficant pathway in the pathophysiology of Pb toxicity. Studies have shown that Pb brings forth increases in interleukin (IL)-10 and tumor necrosis factor-α(TNF-α) in lead-exposed workers. [17; 18]

In addition, lead exposure stimulates the secretion of cytokines, including Interleukin-1 beta (IL-1β) , Interleukin-12p70 (IL-12p70), and Interferon-gamma (IFN-γ) [19].

A study by Yucesoy and colleagues found that that chronic exposure to Pb resulted in alterations in cytokine levels with serum IL-1β levels and IFN-γ decreasing, while IL-2 and TNF-α levels staying consistent. [20]

Other studies have found that Pb increases the percentage of immune cells, such as peripheral cluster of differentiation 4 (CD4+) and cluster of differentiation 8 (CD8+) central memory T cells.[21] Other studies have found that Pb exposed workers had significantly decreased levels of Immunoglobulin G (IgG), Immunoglobulin M (IgM), C3, and C4 complement compared to healthy controls.[22]

Elevated liver enzymes often indicate inflammation or damage to cells in the liver. Inflamed or injured liver cells release high amounts liver enzymes, into the bloodstream.The elevated liver enzymes most commonly found are: Alanine transaminase (ALT), Aspartate transaminase (AST), Alkaline phosphatase (ALP) and Gamma-glutamyl transferanse (GGT).

The potential effects of Pb on liver injury enzymes, such as ALT, and AST have been shown in various studies. In a study by Onyeneke et al.[23], of Nigerian adults, they found that ALT and AST were more elevated in in Pb exposed workers as compared to controls. Regarding GGT and its relationship with Pb exposure in adults, Lee et al. using National Health and Nutrition Examination Survey (NHANES) III data, found associations between blood lead levels (BLL) and GGT[24]. Al-Neamy et al.[25], determined that mean AST, ALT, total bilirubin, and GGT levels were different in Pb exposed as compared to unexposed individuals. ALP was found to be higher in the exposed compared to the unexposed, with the difference showing statistical significance. Obeng-Gyasi and colleagues using data from a representative sample of US adults, found that BLLs were significantly associated with ALP, GGT, and Total bilirubin.[26]

Nonalcoholic fatty liver disease (NAFLD) is common in countries where the Standard American Diet (SAD) is common and can lead to cirrhosis which is irreversible. [27] Pb exposure has been associated with NALFD. In a study by Zhai and colleagues on Chinese residents, elevated BLL was correlated with an elevated probability of NAFLD, with the correlation being strongest among women.[28] Similar results have been found in other populations. [29] Indeed, advanced liver fibrosis is more common in NAFLD in those with elevated Pb exposure.[30]

3. SARS-CoV-2 and Liver Injury

3.1 SARS-CoV-2 *entry and impact on the liver*

Angiotensin-converting enzyme 2 (ACE2) receptor is how SARS-CoV-2 enters host cells. SARS-CoV-2 potentially attaches to ACE2 receptors more extensively when compared to prior coronaviruses, permitting its wide-ranging transmission. [31]

ACE2 is present in the liver. The extent of ACE2 receptor density in the liver is still being explored, with recent reports, using single-cell RNA sequencing indicating that cholangiocytes contain the most significant amount of ACE2 receptors. [32-34]

Cholangiocytes are a diverse group of epithelial cells that line the biliary tree. Their primary physiologic function involves the alteration of hepatic canalicular bile as it is moved in the biliary tree.

3.2 Effects of Sars COV-2 and lead on liver dysfunction

Liver injury is a common characteristic in COVID-19 and is associated with adverse clinical manifestations and potentially mortality.[35; 36] In a study by Wanner and colleagues, they found that abnormal liver function tests were widespread in COVID-19 in two patients with COVID-19 needing hospitalization.[37] In addition, autopsy sections taken from another patient cohort, they presented proof of SARS-CoV-2 liver tropism in

addition to viral RNA recognition in sixty-nine percent of autopsy liver tissue. Finally, they successfully isolated SARS-CoV-2 in liver tissue.

SARS-CoV-2 infection is possibly correlated with acute-on-chronic liver failure, a syndrome that in prevalent in patients with chronic liver disease. This is apparent in patients with cirrhosis and produces extremely elevated mortality in patients with alcohol-related liver disease. Viral infection of the liver with SARS-CoV-2 is an issue still being explored, with direct viral infection possibly triggering liver dysfunction in SARS-CoV-2. [38]

Mechanisms of importance regarding the impact on liver dysfunction among those exposed to SARS-CoV-2 perhaps consist of thrombosis and endothelial-mediated inflammation, which have been implicated in the pathophysiology of portal hypertension and nonalcoholic steatohepatitis.[39; 40] Overall, the mechanism of liver dysfunction in COVID-19 infection is believed to be multifactorial and related to cytokine storm, immune dysregulation, and ischemic injury.

Portal or sinusoidal vascular thrombosis has been reported in 50% of patients in recent postmortem liver biopsies from patients with COVID-19. [41]The study also provided potential evidence for an association between liver vascular thrombosis, coagulopathy, and liver injury in those with SARS-CoV-2 infection, as demonstrated by high D-dimer and ALT levels. [41]Platelet-fibrin microthrombi have been noted in COVID-19-affected livers at autopsy with hepatic sinusoids and portal vein platelet aggregates.[42]

Hepatic steatosis is a common characteristic in the liver pathology of COVID-19-affected individuals; this may be due to coagulation's activation that drives hepatic steatosis. [43]

The mechanism of Plasminogen activator inhibitor-1 (PAI-1) involvement in COVID-19-induced liver dysfunction potentially involves PAI-1 has been correlated with NASH and NAFLD. [44; 45] PAI-1 is an indicator of endothelial cell damage. [46] When existing in excess, PAI-1 binds to TLR4 on macrophages, bringing forth the secretion of proinflammatory chemokines and cytokines. [47]PAI-1 elevation occurs due to Interleukin 6 (IL-6) signaling to vascular cells in COVID-19. In the liver, this potentially brings forth microvascular thrombosis, steatosis, and inflammation. Patients with COVID-19 with liver injury potentially have demonstrated elevated levels of serum markers of hypercoagulability, increased IL-6, increased platelet accumulation, and increased Liver sinusoidal endothelial cells injury manifested as increased Von Willebrand factor (vWF), and neutrophil infiltration in liver histology. [48]

3.3 Possible causes of elevated liver enzymes in SARS-CoV-2

The possible causes of higher levels on injury enzymes in those afflicted with SARS-CoV-2 are still under review. Possible mechanisms of action include damage that promotes liver injury primarily due to shock/hypoxia, even though a direct effect of SARS-CoV-2 on the liver is also under consideration mechanistically. [49; 50]

Liver injury, demonstrated through abnormal injury enzymes, is a conventional clinical element of COVID-19 in patients with the disease needing hospitalization.

Autopsy samples have provided extensive evidence for SARS-CoV-2 liver tropism, as well as viral RNA recognition in sixty-nine percent of autopsy liver specimens and isolation of infectious SARS-CoV-2 from liver tissue postmortem. Additionally, transcription-, proteomic- and transcription factor-based activity profiles in hepatic autopsy samples have revealed parallels to the signatures related to additional human liver viral infections. [37]

There are many studies of elevated liver injury markers and liver dysregulation in SARS-CoV-2 affected individuals, which manifest as high monocyte chemoattractant protein 1 (MCP1) gamma-glutamyl transferase (GGT), alanine transaminase (ALT), and bilirubin. When analyzed in the context of diminished amounts of albumin, this indicates liver damage with potential damage to biliary cells. [51]

4. Interaction between Lead and SARS-CoV-2 in liver injury

The potential interaction of Pb and SARS-CoV-2 and its effects of the liver are summarized in Figure 1.

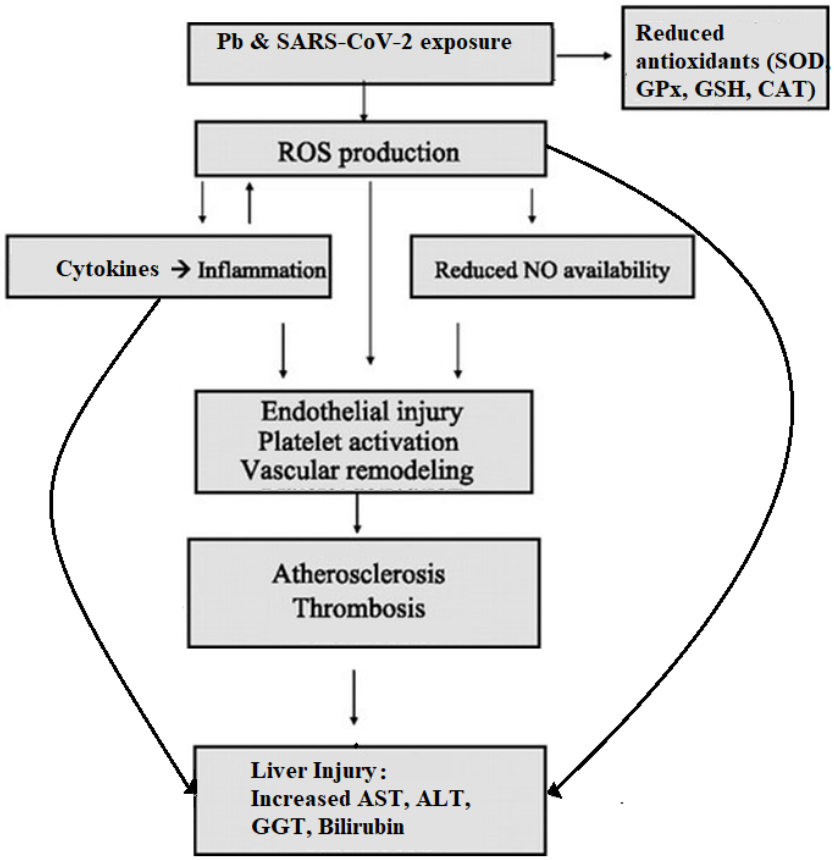

Figure 1. Critical factors in the mechanism of the combined effect of Pb and SARS CoV-2

The hypothesized effects of the interaction of Pb and SARS-CoV-2 on liver dysfunction are potentially extensive but must focus on immune cell responses. Exposure to environmental toxicants such as Pb has been linked with changes in the immune system. [52; 53]Pb exposure may increase individuals' susceptibility to infection, thus lengthening recovery from infection and potentially diminishing the effects of vaccinations. Pb exposure has also been associated with the promotion of immune system dysfunction; environmental exposure to Pb thus may decreases immune responses in addition to potentially increasing the odds of infectious diseases such as COVID-19.[54-56]

Many cytokines such as nuclear factor kappa B (NFκB), IL-6, and tumor necrosis factor-alpha (TNFα) released from SARS-CoV-2-infected monocytes, and macrophages may lead to injurious cascades derived from inflammation causing injury to organs such as the liver. [57]

The immunotoxic effects of Pb are multifaceted and may include the promotion of T helper *2* (Th-2) development by limiting T helper*1* (Th-1) cell proliferation. [58] In addition, pb potentially adversely alters a protective immune response, particularly in organs with highly expressed ACE2 receptors, such as the liver, via interactions with the aryl hydrocarbon receptor (AhR).[59]

Pb can cause ROS and oxidative stress by partaking in Fenton- and Haber-Weiss-type reactions. In addition, Pb may bring forth oxidative stress in Vascular smooth muscle cells (VSMC) and endothelial cells. Oxidative stress can result in inflammation, apoptosis, and fibrosis by triggering NF-κB, which is the critical transcription factor for many proinflammatory cytokines, chemokines, and adhesion molecules. Pb also potentially

reduces antioxidants such as Superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione (GSH), and catalase (CAT).

Normal endothelial lining averts thrombosis by many mechanisms: *1*) endothelial surface coating by Heparan Sulfate Proteoglycans (HSPG). HSPG has heparin-like anticoagulant properties, *2*) Promotion of fibrinolysis (via i.e., Tissue plasminogen activator - t-PA) , *3*) endothelium-derived activation of a potent inhibitor of platelet adhesion and activation - Nitric Oxide-NO and *4*) prostacyclin. [60] Pb exposure potentially harms the endothelium, decreases HSPG production, prevents endothelial repair, and reduces NO availability via ROS-mediated NO inactivation.[61]

Using fetal lung fibroblasts and cultured human aorta smooth muscle cells, Yamamoto and colleagues [62] showed that Pb chloride triggers, in a dose-dependent manner, a significant inhibition of t-PA and a substantial elevation in PAI-1 production in cultured fibroblasts. Also, Pb-exposed smooth muscle cells demonstrated a substantial dose-dependent decrease in t-PA production and, to a less significant degree, PAI-1 production. Therefore, the interaction of the cellular components of the subendothelial tissue with Pb appears to move the equilibrium of antifibrinolytic and fibrinolytic influences in support of the latter, thus increasing the probability of thrombosis.[60]

5. Conclusions

In sum, the interaction of Pb and SARS CoV-2 and its impact on the liver is hypothesized to be through the promotion of ROS production and oxidative stress in addition to inflammation.

Cytokines, including IL-6, (NFκB), and TNFα released from SARS-CoV-2-infected macrophages and monocytes, potentially lead to inflammation-derived injurious cascades that promote liver dysfunction. Pb likewise potentially promotes ROS production and oxidative stress. In addition, oxidative stress may promote inflammation, fibrosis, and apoptosis by activating NF-κB and subsequent production of proinflammatory cytokines, adhesion molecules, and chemokines.

These factors hypothetically bring forth liver injury enzymes such as gamma-glutamyl transferase (GGT) and alanine transaminase (ALT). This interaction may result in high D-dimer and elevated liver injury enzymes such as alanine aminotransferase (ALT), contributing to thrombosis, coagulopathy, and liver dysfunction.

Another effect of combined exposure theoretically includes endothelial-mediated inflammation and thrombosis, which has been linked to NASH. The role of PAI-1 in the disease and Pb-induced liver injury is hypothetically interesting as both have been shown to increase PAI-1, and increased PAI-1 has been correlated with NASH and NAFLD.

Finally, it must be noted that other heavy metals including cadmium, arsenic, and mercury have similar properties to Pb and would also promote respiratory toxicity, affect viral disease, antifviral immunity, and immuntoxicity thus, exposure to all metals must be limited.[63]

Conflicts of Interest: The author(s) declare no conflict of interest

Availability of data and materials: The data that support the findings of this study are available from the corresponding author at reasonable request.

References:

1. Lai, C.-C., Shih, T.-P., Ko, W.-C., Tang, H.-J. and Hsueh, P.-R. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. International journal of antimicrobial agents, **2020** ,*55* , 105924.
2. Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J. and Gu, X. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet, **2020** ,*395* , 497-506.
3. Du Toit, A. Outbreak of a novel coronavirus. Nature Reviews Microbiology, **2020** , *18* , 123-123.

4. announces COVID, W., outbreak a pandemic. Europe: World Health Organization, 2020 [cited 2020 Apr 18].
5. Perlman, S., Another decade, another coronavirus. Mass Medical Soc; 2020; 760-762.
6. Hui, D.S., Azhar, E.I., Kim, Y.-J., Memish, Z.A., Oh, M.-d. and Zumla, A. Middle East respiratory syndrome coronavirus: risk factors and determinants of primary, household, and nosocomial transmission. The Lancet Infectious Diseases, **2018** , *18* , e217-e227.
7. Zhao, S., Lin, Q., Ran, J., Musa, S.S., Yang, G., Wang, W., Lou, Y., Gao, D., Yang, L. and He, D. Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: A data-driven analysis in the early phase of the outbreak. International journal of infectious diseases, **2020** ,*92* , 214-217.
8. Ginzburg, A.V., Ginzburg, V.V., Ginzburg, J.O., Arias, A.G. and Rakesh, L. Modeling the Dynamics of the Coronavirus SARS-CoV-2 Pandemic using Modified SIR Model with the'Damped-Oscillator'Dynamics of the Effective Reproduction Number. arXiv preprint arXiv:2205.14747,**2022** .
9. Roy, A., Bellinger, D., Hu, H., Schwartz, J., Ettinger, A.S., Wright, R.O., Bouchard, M., Palaniappan, K. and Balakrishnan, K. Lead exposure and behavior among young children in Chennai, India. Environmental health perspectives, **2009** , *117* , 1607-1611.
10. He, K., Wang, S. and Zhang, J. Blood lead levels of children and its trend in China. Science of the Total Environment, **2009** ,*407* , 3986-3993.
11. Pfadenhauer, L.M., Burns, J., Rohwer, A. and Rehfuess, E.A. Effectiveness of interventions to reduce exposure to lead through consumer products and drinking water: a systematic review. Environmental research, **2016** , *147* , 525-536.
12. Flora, G., Gupta, D. and Tiwari, A. Toxicity of lead: a review with recent updates. Interdisciplinary toxicology, **2012** , *5* , 47.
13. Prevention, C.f.D.C.a., Chronic Liver Disease and Cirrhosis.
14. Darwish, W.S. and Ikenaka, Y. Biological responses of xenobiotic metabolizing enzymes to lead exposure in cultured H4IIE rat. Japanese Journal of Veterinary Research, **2013** , *61* , S48-S53.
15. Hsu, P.-C. and Guo, Y.L. Antioxidant nutrients and lead toxicity. Toxicology, **2002** , *180* , 33-44.
16. Thapa, B. and Walia, A. Liver function tests and their interpretation. The Indian Journal of Pediatrics, **2007** , *74* , 663-671.
17. Mishra, K., Chauhan, U. and Naik, S. Effect of lead exposure on serum immunoglobulins and reactive nitrogen and oxygen intermediate. Human & experimental toxicology, **2006** , *25* , 661-665.
18. Valentino, M., Rapisarda, V., Santarelli, L., Bracci, M., Scorcelletti, M., Di Lorenzo, L., Cassano, F. and Soleo, L. Effect of lead on the levels of some immunoregulatory cytokines in occupationally exposed workers. Human & experimental toxicology,**2007** , *26* , 551-556.
19. Huo, X., Dai, Y., Yang, T., Zhang, Y., Li, M. and Xu, X. Decreased erythrocyte CD44 and CD58 expression link e-waste Pb toxicity to changes in erythrocyte immunity in preschool children. Science of the Total Environment, **2019** , *664* , 690-697.
20. Metryka, E., Chibowska, K., Gutowska, I., Falkowska, A., Kupnicka, P., Barczak, K., Chlubek, D. and Baranowska-Bosiacka, I. Lead (Pb) exposure enhances expression of factors associated with inflammation. International journal of molecular sciences, **2018** , *19* , 1813.
21. Cao, J., Xu, X., Zhang, Y., Zeng, Z., Hylkema, M.N. and Huo, X. Increased memory T cell populations in Pb-exposed children from an e-waste-recycling area. Science of the Total Environment,**2018** , *616* , 988-995.
22. Ündeger, Ü., Başaran, N., Canpmar, H. and Kansu, E. Immune alterations in lead-exposed workers. Toxicology, **1996** , *109* , 167-172.
23. Onyeneke, E.C. and Omokaro, E.U. Effect of occupational exposure to lead on liver function parameters. Int. J. Pharm. Med. Sci,**2016** , *6* , 15-19.
24. Lee, D.-H., Lim, J.-S., Song, K., Boo, Y. and Jacobs Jr, D.R. Graded associations of blood lead and urinary cadmium concentrations with oxidative-stress–related markers in the US population: Results from the Third National Health and Nutrition Examination Survey. Environmental health perspectives,

2006 , *114* , 350-354.

25. Al-Neamy, F., Almehdi, A., Alwash, R., Pasha, M., Ibrahim, A. and Bener, A. Occupational lead exposure and amino acid profiles and liver function tests in industrial workers. International Journal of Environmental Health Research, **2001** , *11* , 181-188.
26. Obeng-Gyasi, E., Armijos, R.X., Weigel, M.M., Filippelli, G. and Sayegh, M.A. Hepatobiliary-related outcomes in US adults exposed to lead. Environments, **2018** , *5* , 46.
27. Foulds, C.E., Treviño, L.S., York, B. and Walker, C.L. Endocrine-disrupting chemicals and fatty liver disease. Nature Reviews Endocrinology, **2017** , *13* , 445-457.
28. Zhai, H., Chen, C., Wang, N., Chen, Y., Nie, X., Han, B., Li, Q., Xia, F. and Lu, Y. Blood lead level is associated with non-alcoholic fatty liver disease in the Yangtze River Delta region of China in the context of rapid urbanization. Environmental Health, **2017** ,*16* , 1-9.
29. Nguyen, H.D. and Kim, M.-S. Cadmium, lead, and mercury mixtures interact with non-alcoholic fatty liver diseases. Environmental Pollution, **2022** , *309* , 119780.
30. Reja, D., Makar, M., Visaria, A., Karanfilian, B. and Rustgi, V. Blood lead level is associated with advanced liver fibrosis in patients with non-alcoholic fatty liver disease: A nationwide survey (NHANES 2011–2016). Annals of Hepatology, **2020** , *19* , 404-410.
31. Yeo, C., Kaushal, S. and Yeo, D. Enteric involvement of coronaviruses: is faecal–oral transmission of SARS-CoV-2 possible? The lancet Gastroenterology & hepatology, **2020** , *5* , 335-337.
32. Li, J. and Fan, J.-G. Characteristics and mechanism of liver injury in 2019 coronavirus disease. Journal of Clinical and Translational Hepatology, **2020** , *8* , 13.
33. Xu, L., Liu, J., Lu, M., Yang, D. and Zheng, X. Liver injury during highly pathogenic human coronavirus infections. Liver international,**2020** , *40* , 998-1004.
34. Chai, X., Hu, L., Zhang, Y., Han, W., Lu, Z., Ke, A., Zhou, J., Shi, G., Fang, N. and Fan, J. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. biorxiv,**2020** .
35. Saviano, A., Wrensch, F., Ghany, M.G. and Baumert, T.F. Liver disease and coronavirus disease 2019: from pathogenesis to clinical care. Hepatology, **2021** , *74* , 1088-1100.
36. Hundt, M.A., Deng, Y., Ciarleglio, M.M., Nathanson, M.H. and Lim, J.K. Abnormal liver tests in COVID-19: a retrospective observational cohort study of 1,827 patients in a major US hospital network. Hepatology,**2020** , *72* , 1169-1176.
37. Wanner, N., Andrieux, G., Badia-i-Mompel, P., Edler, C., Pfefferle, S., Lindenmeyer, M.T., Schmidt-Lauber, C., Czogalla, J., Wong, M.N. and Okabayashi, Y. Molecular consequences of SARS-CoV-2 liver tropism. Nature metabolism, **2022** , *4* , 310-319.
38. Marjot, T., Webb, G.J., Barritt, A.S., Moon, A.M., Stamataki, Z., Wong, V.W. and Barnes, E. COVID-19 and liver disease: mechanistic and clinical perspectives. Nature reviews Gastroenterology & hepatology,**2021** , *18* , 348-364.
39. Furuta, K., Guo, Q., Pavelko, K.D., Lee, J.-H., Robertson, K.D., Nakao, Y., Melek, J., Shah, V.H., Hirsova, P. and Ibrahim, S.H. Lipid-induced endothelial vascular cell adhesion molecule 1 promotes nonalcoholic steatohepatitis pathogenesis. The Journal of clinical investigation, **2021** , *131* .
40. McConnell, M.J., Kondo, R., Kawaguchi, N. and Iwakiri, Y. Covid-19 and Liver Injury: Role of Inflammatory Endotheliopathy, Platelet Dysfunction, and Thrombosis. Hepatology Communications, **2022** ,*6* , 255-269.
41. Sonzogni, A., Previtali, G., Seghezzi, M., Grazia Alessio, M., Gianatti, A., Licini, L., Morotti, D., Zerbi, P., Carsana, L. and Rossi, R. Liver histopathology in severe COVID 19 respiratory failure is suggestive of vascular alterations. Liver International,**2020** , *40* , 2110-2116.
42. Rapkiewicz, A.V., Mai, X., Carsons, S.E., Pittaluga, S., Kleiner, D.E., Berger, J.S., Thomas, S., Adler, N.M., Charytan, D.M. and Gasmi, B. Megakaryocytes and platelet-fibrin thrombi characterize multi-organ thrombosis at autopsy in COVID-19: a case series. EClinicalMedicine,**2020** , *24* , 100434.
43. Kopec, A.K., Abrahams, S.R., Thornton, S., Palumbo, J.S., Mullins, E.S., Divanovic, S., Weiler, H., Owens, A.P., Mackman, N. and Goss, A. Thrombin promotes diet-induced obesity through fibrin-driven inflammation. The Journal of clinical investigation, **2017** ,*127* , 3152-3166.
44. Targher, G., Bertolini, L., Scala, L., Zenari, L., Lippi, G., Franchini, M. and Arcaro, G. Plasma PAI-1

levels are increased in patients with nonalcoholic steatohepatitis. Diabetes care,**2007** , *30* , e31-e32.
45. Chang, M.L., Hsu, C.M., Tseng, J.H., Tsou, Y.K., Chen, S.C., Shiau, S.S., Yeh, C.T. and Chiu, C.T. Plasminogen activator inhibitor-1 is independently associated with non-alcoholic fatty liver disease whereas leptin and adiponectin vary between genders. Journal of gastroenterology and hepatology, **2015** , *30* , 329-336.
46. Kang, S., Tanaka, T., Inoue, H., Ono, C., Hashimoto, S., Kioi, Y., Matsumoto, H., Matsuura, H., Matsubara, T. and Shimizu, K. IL-6 trans-signaling induces plasminogen activator inhibitor-1 from vascular endothelial cells in cytokine release syndrome. Proceedings of the National Academy of Sciences, **2020** , *117* , 22351-22356.
47. Matsuyama, T., Kubli, S.P., Yoshinaga, S.K., Pfeffer, K. and Mak, T.W. An aberrant STAT pathway is central to COVID-19. Cell Death & Differentiation, **2020** , *27* , 3209-3225.
48. McConnell, M.J., Kawaguchi, N., Kondo, R., Sonzogni, A., Licini, L., Valle, C., Bonaffini, P.A., Sironi, S., Alessio, M.G. and Previtali, G. Liver injury in COVID-19 and IL-6 trans-signaling-induced endotheliopathy. Journal of hepatology, **2021** , *75* , 647-658.
49. Fan, Z., Chen, L., Li, J., Cheng, X., Yang, J., Tian, C., Zhang, Y., Huang, S., Liu, Z. and Cheng, J. Clinical features of COVID-19-related liver functional abnormality. Clinical Gastroenterology and Hepatology, **2020** , *18* , 1561-1566.
50. Bangash, M.N., Patel, J. and Parekh, D. COVID-19 and the liver: little cause for concern. The lancet Gastroenterology & hepatology,**2020** , *5* , 529-530.
51. Morgan, K., Samuel, K., Vandeputte, M., Hayes, P.C. and Plevris, J.N. SARS-CoV-2 infection and the liver. Pathogens, **2020** ,*9* , 430.
52. Bornstein, S.R., Voit-Bak, K., Schmidt, D., Morawietz, H., Bornstein, A.B., Balanzew, W., Julius, U., Rodionov, R.N., Biener, A.M. and Wang, J. Is there a role for environmental and metabolic factors predisposing to severe COVID-19? Hormone and Metabolic Research,**2020** , *52* , 540-546.
53. Kwak, E.S., Just, A., Whyatt, R. and Miller, R.L. Phthalates, pesticides, and bisphenol-A exposure and the development of nonoccupational asthma and allergies: how valid are the links? The Open Allergy Journal, **2009** , *2* , 45.
54. Bulka, C.M., Bommarito, P.A., Aiello, A.E. and Fry, R.C. Cytomegalovirus seroprevalence, recurrence, and antibody levels: Associations with cadmium and lead exposures in the general United States population. Environmental Epidemiology, **2020** ,*4* .
55. Emeny, R.T., Korrick, S.A., Li, Z., Nadeau, K., Madan, J., Jackson, B., Baker, E. and Karagas, M.R. Prenatal exposure to mercury in relation to infant infections and respiratory symptoms in the New Hampshire Birth Cohort Study. Environmental research, **2019** ,*171* , 523-529.
56. Krueger, W.S. and Wade, T.J. Elevated blood lead and cadmium levels associated with chronic infections among non-smokers in a cross-sectional analysis of NHANES data. Environmental Health,**2016** , *15* , 1-13.
57. Iwasaki, M., Saito, J., Zhao, H., Sakamoto, A., Hirota, K. and Ma, D.J.I. Inflammation triggered by SARS-CoV-2 and ACE2 augment drives multiple organ failure of severe COVID-19: molecular mechanisms and implications. **2021** , *44* , 13-34.
58. Fenga, C., Gangemi, S., Di Salvatore, V., Falzone, L. and Libra, M. Immunological effects of occupational exposure to lead. Molecular medicine reports, **2017** , *15* , 3355-3360.
59. Tsatsakis, A., Petrakis, D., Nikolouzakis, T.K., Docea, A.O., Calina, D., Vinceti, M., Goumenou, M., Kostoff, R.N., Mamoulakis, C. and Aschner, M. COVID-19, an opportunity to reevaluate the correlation between long-term effects of anthropogenic pollutants on viral epidemic/pandemic events and prevalence. Food and Chemical Toxicology,**2020** , *141* , 111418.
60. Vaziri, N.D. Mechanisms of lead-induced hypertension and cardiovascular disease. American Journal of Physiology-Heart and Circulatory Physiology, **2008** , *295* , H454-H465.
61. Vaziri, N.D., Liang, K. and Ding, Y. Increased nitric oxide inactivation by reactive oxygen species in lead-induced hypertension. Kidney international, **1999** , *56* , 1492-1498.
62. Yamamoto, C., Miyamoto, A., Sakamoto, M., Kaji, T. and Kozuka, H. Lead perturbs the regulation of spontaneous release of tissue plasminogen activator and plasminogen activator inhibitor-1 from vascular

smooth muscle cells and fibroblasts in culture. Toxicology, **1997** ,*117* , 153-161.
63. Skalny, A.V., Lima, T.R.R., Ke, T., Zhou, J.-C., Bornhorst, J., Alekseenko, S.I., Aaseth, J., Anesti, O., Sarigiannis, D.A. and Tsatsakis, A. Toxic metal exposure as a possible risk factor for COVID-19 and other respiratory infectious diseases. Food and Chemical Toxicology, **2020** , *146* , 111809.