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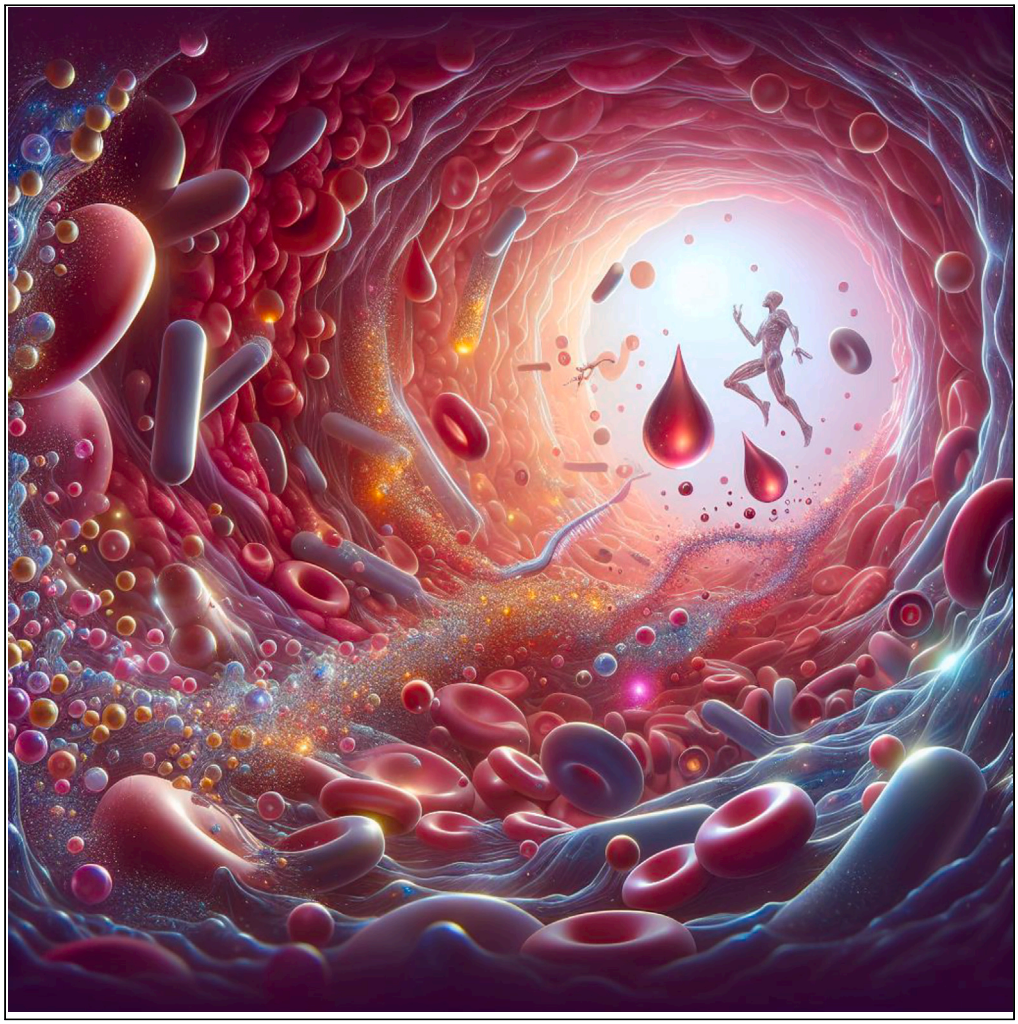

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Highlights

The presence of gallium-base liquid metals (Ga/GaIn/GaInSn) does not induce hemolysis

Liquid metals have no significant effect on the components in blood and serum

Surface interface of liquid metal does not change significantly after contacting blood

Wang et al., iScience 27, 111183
November 15, 2024
https://doi.org/10.1016/j.isci.2024.111183

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The biocompatibility of gallium-based liquid metals with blood and serum

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SUMMARY

Excellent biocompatibility of liquid metals is the basis for developing biomedical applications, such as implantable devices, drug delivery, and tumor therapy. Especially, a systematic study to reveal the influence of gallium-based liquid metals on the composition of blood while they are used in the human body is vital but missing. Here, the compatibility of three kinds of frequently used gallium-based liquid metals with human blood and serum was explored systematically. The results show that treating blood and serum with gallium-based liquid metals did not cause hemolysis, suggesting red blood cells are not damaged or ruptured, and treatment had a negligible effect on the components in the blood. Additionally, the serum levels of glucose, cholesterol, and liver function molecules showed no change after adding liquid metals. These findings suggest that liquid metals have high compatibility with human blood and serum and are conductive to be applied in the fields of biomedical engineering.

INTRODUCTION

Gallium-based liquid metals (GLMs) currently have drawn increasing attention in the biomedical engineering area,[1–8] due to their unique and excellent properties, such as electrical and thermal conductivity, fluidity, and deformability, especially the favorable biocompatibility.[9–12] Such materials have been increasingly explored as implantable electrodes,[13–15] drug carriers,[3,16] embolic agents,[17] wound adjuvant[18] and reaction platform[19–21] and so on.[22–24] Importantly, functional molecules could be bound with GLMs via an oxide layer produced on the surface in an aerobic environment, which enabled GLMs to load drugs or heal wounds for clinical potential. Currently, it has been found that the oxide layer could be connected with -SH and -OH by forming metallic thiol bonds and hydrogen bonds.[25,26] Except that, it could also form π-π, electrostatic interaction, or intercalative binding to construct various composites for biomedical engineering applications.[22]

As for the wide exploration in the medical field, it is concerned that such materials have unfavorable effects on the human body. First of all, there are many components in blood or serum, including red blood cells (RBC), white blood cells (WBC), platelets (PLT), hemoglobin, cholesterol, alanine transaminase, glucose, and so forth, which are closely related to health and could be detected to monitor physical health.[27–29] For example, WBC could reflect the body's immune capacity. PLT is involved in the hemostasis and coagulation of the human body. Hemoglobin (HGB) could transport oxygen, which is a good indication of the degree of anemia. Moreover, some components are related to organ function, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are related to the liver, urea and uric acid (UA) are related to the kidney, and so on. Accordingly, it is reasonable to speculate that the liquid metal may combine with molecules in the blood and thus affect the composition of the blood, which will lead to blood disorders and further affect health. Even though there are a few articles that have explored biocompatibility with mice or other animals,[16] there is a lack of research involving humans, which may differ to some extent. Therefore, it is necessary to reveal the influence and action of gallium-based liquid metal on the composition of blood while GLMs are used in the human body for biomedical engineering applications. However, it has not been studied in detail, which will hinder its real clinical application.

Herein, the effect of gallium-based liquid metals including gallium (Ga), gallium-indium (GaIn) and galinstan (GaInSn) on human whole blood and components in serum were studied systematically. The blood routine and biochemical analyzer were used to analyze the effect of liquid metal on composites in blood and serum to distinguish the biocompatibility of gallium-based liquid metals at room temperature *in vitro* experiments. The indexes of liver and kidney functions, glucose, and blood lipids were maintained in the normal range statistically.

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https://doi.org/10.1016/j.isci.2024.111183

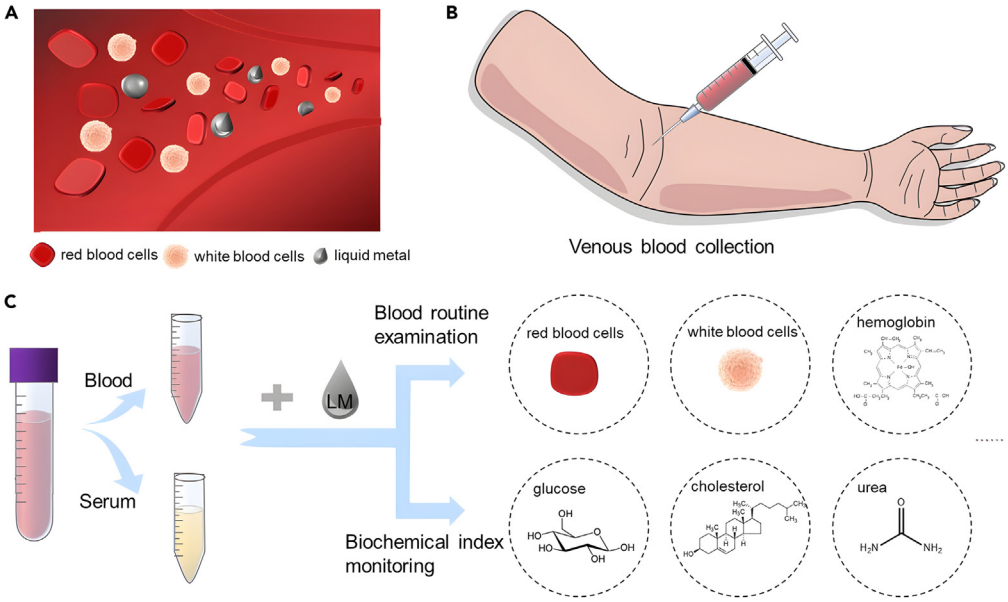

Figure 1. The entire process of detecting liquid metals in blood

(A) Soft liquid metal in blood.

(B) Venous blood collection method.

(C) Blood routine examination and biochemical index monitoring of main factors.

Through the interfacial force analysis, it is proved that the surface bonding on the oxide layer of liquid metal mainly relies on physical interactions of H-bonding, electrostatic interaction, intercalative binding, and so forth, which do not affect the content and function of blood. In addition, Ga/GaInSn were compared, proving that gallium-based alloys have negligible influence on blood or serum. Obviously, this work provides fundamental support for gallium-based liquid metals used in biomedical engineering, such as drug delivery, wound healing, and medical instruments.

RESULTS AND DISCUSSION

Figure 1A and 1B show a schematical diagram of a liquid metal flowing process in blood and the blood drawing. Venous blood samples were obtained and preserved in tubes containing anticoagulants. Thereafter, gallium based liquid metal droplet (Ga/GaIn/GaInSn) was introduced into the blood sample. Then the components pivotal to the health were examined and analyzed. Gallium, known for its reactivity with oxygen, forms an oxidized layer, which is a critical aspect of the study. In addition, gallium also reacts with the H_2O and releases Ga ions.[30] Thus, the following reactions are anticipated to take place in blood.[26,30–32]

$$Ga(l) + O_2(g) \rightarrow Ga_2O_3(s) \quad (1)$$

$$2Ga_2O_3 + H_2O \rightarrow 4GaOOH \quad (2)$$

$$GaOOH + H_2O \rightarrow Ga^{3+} + 3OH^- \quad (3)$$

Effect on components in blood

From the experimental results, we could find that there is no obvious hemolysis after adding Ga/GaIn/GaInSn, as shown in Figure S1. It could be preliminarily determined that liquid metal has certain biocompatibility with blood.

To explore the reaction between liquid metal and blood components, we detected the changes using an analyzer as shown in Figure 2. The detection time, within 8 h, is determined according to the People's Republic of China Health industry standard "Blood Storage Requirements" (WS 399–2023) and the practical advice of doctors in the hospital's clinical laboratory. This ensures that the blood indicators remain normal in external storage environments at normal temperatures. The main components in the blood sample (503) such as red blood cell (RBC) and mean corpuscular hemoglobin (MCH) are not changed with contact time as shown in Figures 2A and S2A. Mean corpuscular volume (MCV, Figure S2B) and hematocrit (HCT, Figure S2C) are increased slightly. While white blood cells (WBC, Figure 2B),

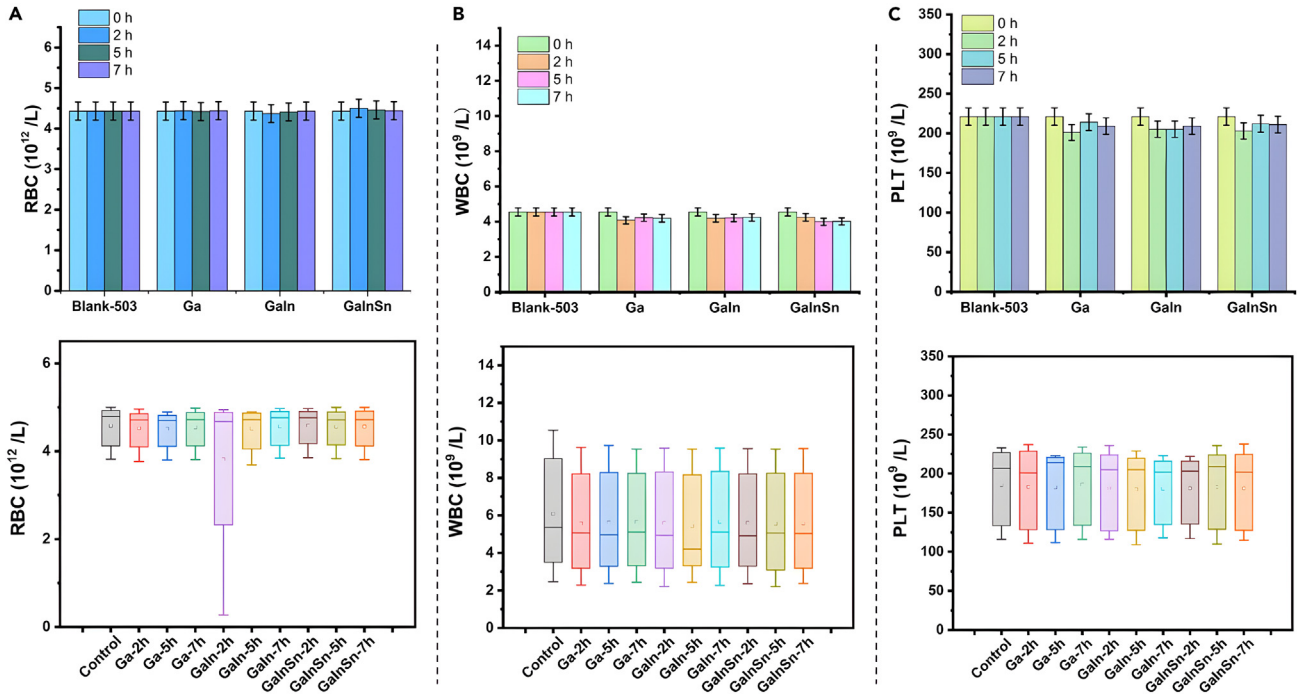

Figure 2. The influence of liquid metal on different components in blood and corresponding analysis of variance

(A) Changes of RBC in blood after contacting with liquid metal (Ga/GaIn/GaInSn) at different times (0 h, 2 h, 5 h, 7 h).

(B) Changes of WBC in blood after contacting with liquid metal (Ga/GaIn/GaInSn) at different times (0 h, 2 h, 5 h, 7 h).

(C) Changes of PLT in blood after contacting with liquid metal (Ga/GaIn/GaInSn) at different times (0 h, 2 h, 5 h, 7 h). Data of distinct samples are presented as mean ± SEM. $n = 5$. The bars represent standard deviations.

hemoglobin (HGB, Figure S2D), mean corpuscular-hemoglobin concentration (MCHC, Figure S2E) and platelet (PLT, Figure 2C) are decreased a little. As shown in Table 1 the components are all kept within the normal range, which is of great significance to human health. Through statistical analysis (one way ANOVA), the effect of liquid metal on the main components is concluded as shown in Figures 2 and S2, and the p value in variance analysis is greater than 0.05 ($p > 0.05$), which means the liquid metal has a negligible effect on the main components in blood. As shown in Figures S3–S6, the effects of liquid metal on the main components in other blood samples (501, 502, 401, 402) are also analyzed, which indicates that the trend is as the same. It should be noted that the boxplots represent the average of several samples. Indeed, when the sample was in contact with GaIn for 2 h, sample 410 showed a decrease in RBC, HCT, and HGB levels (Figure S5), while the other samples were not affected obviously (Figures 2 and S2–S6). We analyzed the reason, on one hand, other indicators in blood are normal indicating that the operation is correct. On the other hand, RBC, HCT, and HGB are related to red blood cells, even though they were decreased at 2 h, it returned to normal levels at 5 h (next detection time). This suggests that the GaIn had no effect on the total amount of components in the blood but could cause a temporary reduction of some components in some people. We hypothesize that the results may be related to individual differences in human blood samples. This is worthy of further study, and we will further verify it in subsequent experiments.

Compared with gallium (Ga), GaIn and GaInSn showed similar stability and safety. It implies that the elements of Ga, In, and Sn in liquid metal are effect-free for the components in blood. As reported in a previous study, various gallium-based alloys own diverse properties[33–35] so that to prepare multifunctional materials that could be applied in different conditions.

Effect on components in serum

To further detect the effect of liquid metal on components in serum, serum biochemical analysis was performed. As shown in Figures 3, S7, and S8, total protein (TP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), urea (UREA), uric acid (UA), creatinine (Crea), creatine kinase (CK), cholesterol (CHO), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), glucose (GLU), iron (Fe), carbon dioxide combining power (CO2CP), hypersensitive C-reactive protein (hs-CRP) and other components (Figure S8) were analyzed. It should be noted that not all blood sample indicators are within the normal range, which does not affect our exploration of the influence of liquid metal on the indicators in the blood. For different samples, the effect of liquid metal on the components shows consistency. The variance analysis indicates that liquid metal has negligible effect on the main components in serum, which means that it has no effect on health when the liquid metal is used *in vivo*. For example, in Figure 3L, the carbon dioxide combining power (CO2CP) concentration of the "Ga - 2h" group in sample 3 is 19.3 mmol/L, which is slightly lower than that of the normal range (20–29 mmol/L) but is clinically

Table 1. The normal range of partial components in blood

	RBC	WBC	HGB	PLT	MCH	MCV	HCT	MCHC
Normal range	3.8–5.1	3.5–9.5	115–150	125–350	27–34	82–100	0.35–0.45	316–354
Unit	10^{12}/L	10^{9}/L	g/L	10^{9}/L	pg	fL	L/L	g/L

acceptable. The decrease in CO2CP concentration indicates a reduction in carbon dioxide binding capacity, which is beneficial for gas exchange.

To elucidate the intrinsic mechanisms of liquid metal interactions within the bloodstream, a systematic investigation was conducted, including three distinct aspects: the analysis of serum constituents, the examination of the liquid metal's surface characteristics, and the study of the oxide layer. Since Ga/GaIn/GaInSn, mentioned above, have no obvious effect on blood composition, in this part, Ga and GaInSn are characterized to observe their surface morphology and to analyze their surface interactions, representatively.

Interfacial and surface analysis

The serum constituents are identified and quantified through the application of biochemical assays. Due to the complexity of blood components, the components—blood routine items and biochemical testing items—do not undergo chemical reactions with liquid metal or its surface (such as gallium oxide). To further investigate the alterations in the surface morphology of the liquid metal subsequent to its exposure to blood and serum, a field-emission scanning electron microscope (FESEM) was employed. Compared with liquid metal in water and normal saline, it could be seen clearly that the surface morphology of LM in blood has more wrinkles (Figure 4A) than liquid metal in water and normal saline (Figure S9). The elements have not changed, and the carbon content has increased slightly. Thus, the wrinkle may be due to repeated washing of the liquid metal removed from the blood. Due to the fact that the surface tension of GaInSn (~535 mN/m) is smaller than that of Ga (~700 mN/m), the surface of Ga in blood exhibits fewer wrinkled patterns than that of the GaInSn in blood, as shown in Figure 4A. This is consistent with previous studies.[36–39] Moreover, to rule out the effects of blood anticoagulants, we compared the characterization of two different anticoagulant tubes (ethylenediaminetetraacetic acid (EDTA) anticoagulant tube and sodium citrate anticoagulant tube). As shown in Figure S10, it could be seen that the surface morphology and elements of LM are consistent, which could be concluded that the anticoagulants (EDTA and sodium citrate) have no effect on liquid metal in blood detection.

Additionally, to delve into the interactions and the oxidation states of the liquid metal in the presence of blood, Fourier Transform Infrared Spectroscopy (FT-IR) was utilized to characterize and analyze the binding states of the elements on the liquid metal's surface. As illustrated in Figure 4B, the FT-IR spectrum was performed using the attenuated total refraction (ATR). As shown in the curves of liquid metal (LM), blood, LM surface in saline, and LM surface in blood, it is obviously observed the change between them. Due to a lot of molecules being in blood, the broad bands observed at around 3285 cm^{-1}, which is related to the O-H stretching vibrations.[22] The O-H stretching vibrations were shown slightly on the LM surface, suggesting the occurrence of hydrogen-bond interactions upon contact with blood. While there are no obvious peaks on the liquid metal surface after contact with saline. After adding LM in blood, the emergence of peaks at approximately 1554 cm^{-1} and 1646 cm^{-1} is attributed to the vibration of -N=N-, -C=C- and -C=O- groups,[22,40,41] which related to the organic compounds, such as glucose, amino acid, cholesterol, and so forth in blood. As the peak position of Ga-OH deformation modes and Ga-O stretching modes on liquid metal surfaces were sensitive to ambient environments, such as pH and thermal treatment,[42] the peak position will be slightly offset. The FT-IR spectra demonstrate that no new types of chemical bonds are formed upon contact with blood, supporting the hypothesis that the interaction between liquid metal and blood is predominantly physical in nature, involving processes such as electrostatic attraction, intercalative binding, and hydrogen bonding, as illustrated in Figure 4C. Therefore, it could be concluded that gallium-based liquid metals have blood compatibility, which is to say that they are non-toxicity to humans in blood. As described before, FT-IR spectroscopy indicates the liquid metal in blood will not cause a chemical reaction so that it has a negligible effect on the blood components. Based on different advantages, such as superior conductivity, reconfigurability, fluidity, ease of preparation, recyclability, and contrast imaging capabilities, gallium-based liquid metals are anticipated to play a significant role in *in vivo* biomedical applications such as drug loading-drug release, implant devices, contrast agent.

Conclusion

In summary, this work systematically studied the effect of liquid metal on human blood/serum components. The characterization results on the surface of liquid metal confirmed the good biocompatibility of the gallium-based liquid metals to blood. The blood routine and biochemical tests experiments after adding liquid metal at different contact times prove that liquid metal has negligible effect on the components in blood and serum. Meanwhile, the surface morphology of liquid metal shows no difference in blood, and the metal could keep a liquid state longer time than in normal saline. The FT-IR results confirmed that there was no chemical reaction between the liquid metal and the components (including blood routine items and biochemical testing items) present in the blood. This means that liquid metal can safely exist within the bloodstream. This finding may extend its application from laboratory to clinic. Of course, it is necessary and valuable to continue increasing the sample size in further work and to collect data from different groups of people for individual index testing research. Above all, this study not only implements comprehensive exploration for blood biocompatibility of liquid metal but also burst more inspiration on liquid metal-based multifunctional materials design, specific molecular detection, and implant devices.

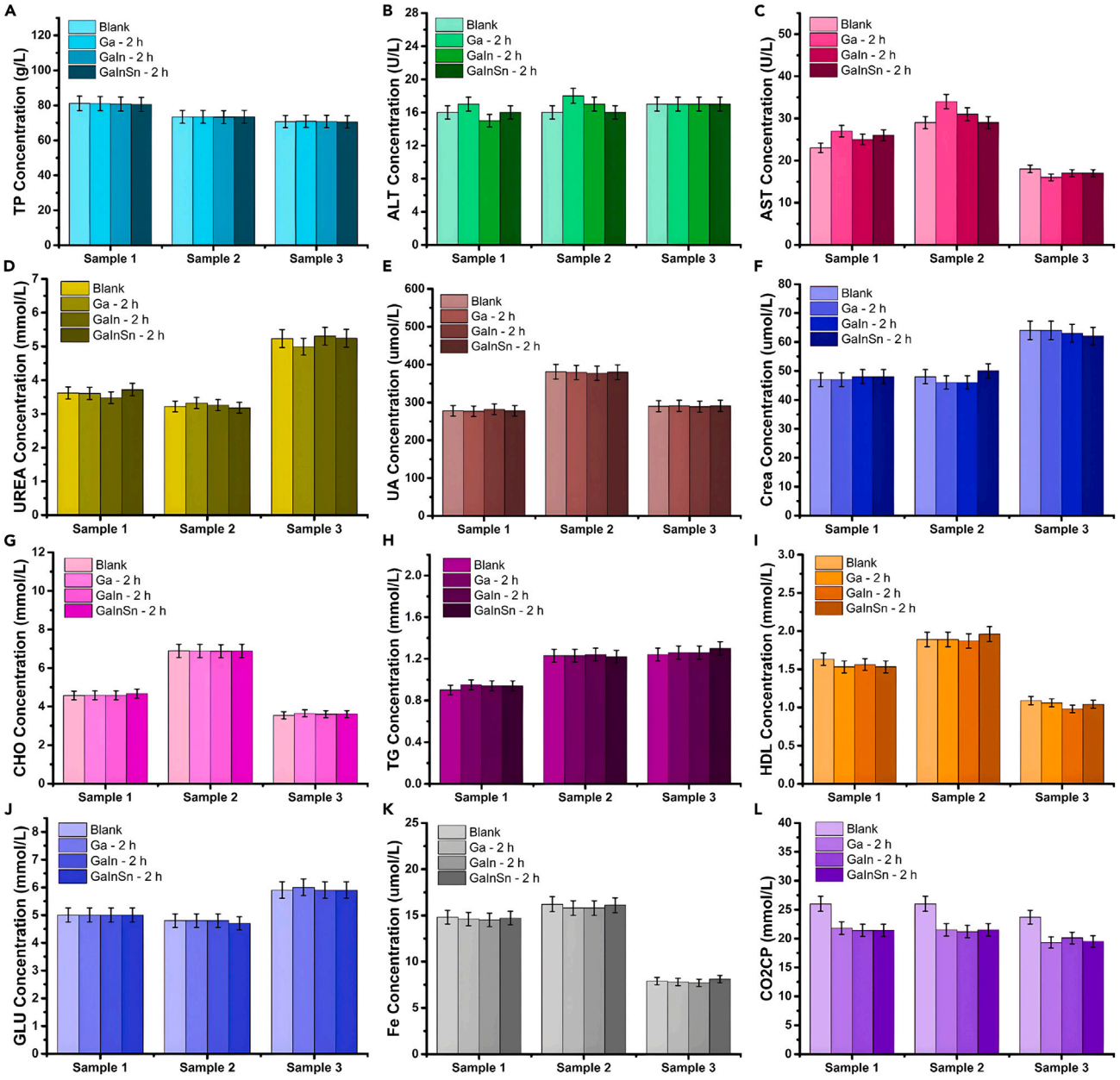

Figure 3. The influence of liquid metal on different components in serum

(A–C) The concentration variation of TP, ALT, and AST related to liver function in serum after exposure to liquid metal 2 h, respectively.

(D–F) The concentration variation of UREA, UA, and Crea related to renal function in serum after exposure to liquid metal for 2 h, respectively.

(G–I) The concentration variation of CHO, TG, and HDL related to blood fat in serum after exposure to liquid metal for 2 h, respectively.

(J–L) The concentration variation of GLU, Fe, and CO2CP in serum after exposure to liquid metal for 2 h, respectively. All data are presented as mean ± SD.

Limitations of the study

Although this study utilizes routine blood tests and biochemical assays for a more detailed analysis of the majority of detection items related to liquid metal in human blood and serum and employs SEM and FT-IR to summarize the interfacial mechanisms, several limitations remain. Firstly, the dataset is insufficiently large, and the classification of different population groups lacks detail. Secondly, the brief preservation time of *ex vivo* blood hinders long-term analysis. Thirdly, the analysis of interfacial mechanisms is not sufficiently in-depth and necessitates further comprehensive examination with advanced equipment. In summary, this article opens a window into the study and application of liquid metal within the human body, yet further in-depth exploration and analysis require continuous refinement.

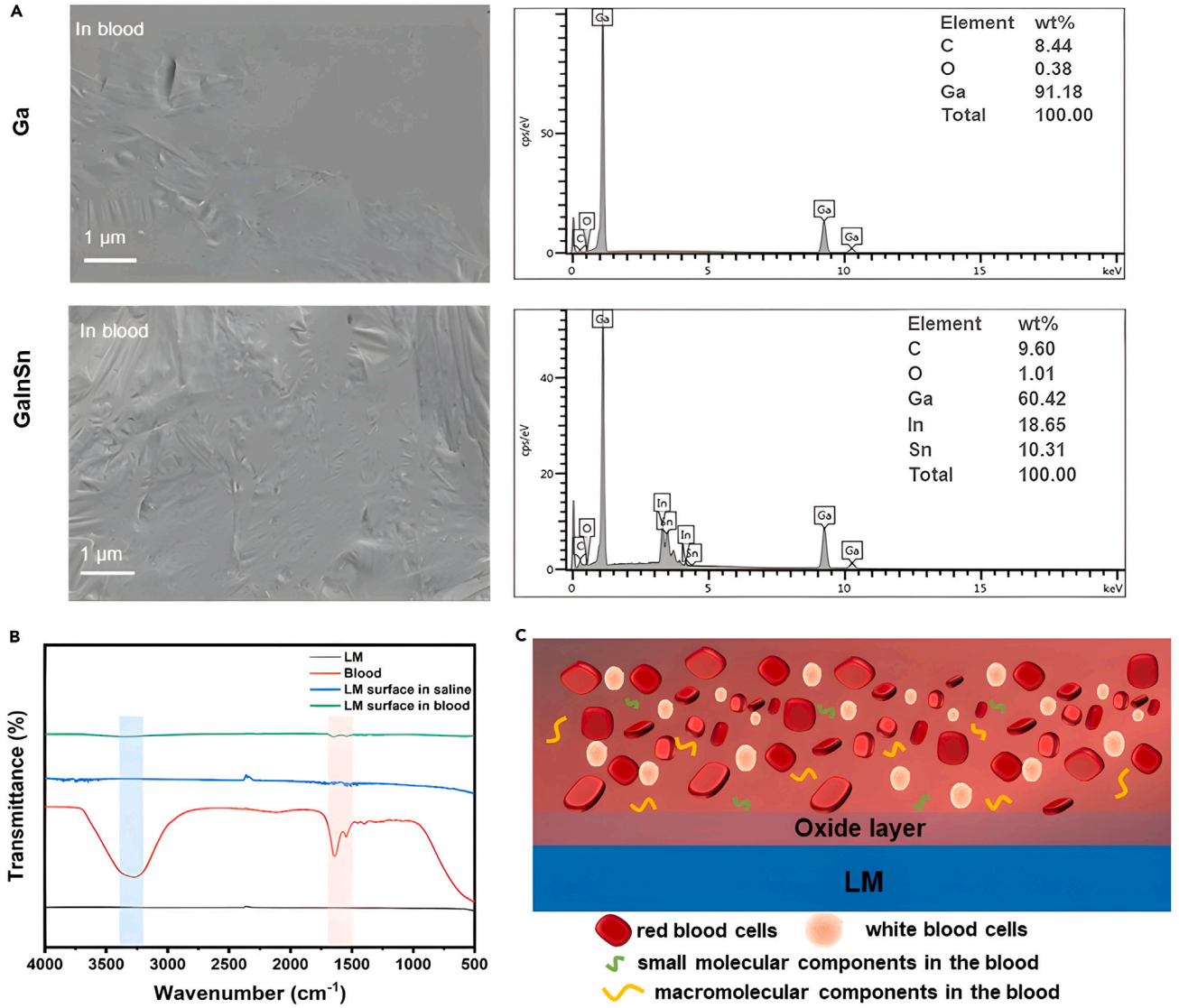

Figure 4. Analysis of interface properties and mechanism of liquid metals in blood

(A) The surface morphology of liquid metal (Ga and GaInSn).

(B) FT-IR spectrum of LM, blood, LM surface in saline and LM surface in blood.

(C) Contact interface between liquid metal and blood.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the Lead Contact, Hongzhang Wang (wanghz@sz.tsinghua.edu.cn).

Materials availability

This study did not generate new unique materials.

Data and code availability

- The data underlying this study are available in the article and supplemental information.
- This article does not report the original code.
- Any additional information required to reanalyze the data reported in this article is available from the lead contact upon request.

ACKNOWLEDGMENTS

This work is supported by the National Natural Science Foundation of China (Grant No. 52405315, No. 52301193), Shandong Provincial Natural Science Foundation (ZR2024QE197), the Research Start-up Funds for Recruited Talents of University of Health and Rehabilitation Sciences (KWXZ 2023026) and Funded with the Marine Natural Products R&D Laboratory, Tsinghua SIGS Cross-disciplinary Research and Innovation Fund (JC2024006), Qingdao Key Laboratory (QDSHYTRCWYJKF 2024-01). And I would like to express my heartfelt thanks here for the guidance by Dr. Xinyu Liu, chief physician of the National Rehabilitation AIDS Center for blood and serum index analysis, and thanks to Dr. Run Liu and Dr. Jiankang Liu for supporting the revision of the article.

AUTHOR CONTRIBUTIONS

X. Wang and H. Wang conceived the idea and designed the experiments. X. Wang executed the experiments, analyzed the data, and wrote the article. Y. He and Y. Wu assisted with the characterization experiment. Z. Qi took blood samples. Y. Wang and J. Ding provide useful platform and resources. J. Zhang, Y. Fan, and H. Wang assisted in the analysis and reviewed the article. All authors discussed the experiments and gave consent for this publication.

DECLARATION OF INTERESTS

The authors declare no competing interests.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS
  - Materials
- METHOD DETAILS
  - Characterization
  - Composition test in blood/serum
- QUANTIFICATION AND STATISTICAL ANALYSIS

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2024.111183.

Received: June 17, 2024
Revised: August 12, 2024
Accepted: October 14, 2024
Published: October 16, 2024

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Biological samples		
Blood	Affiliated Hospital	Ethics Committee of University of Health and Rehabilitation Sciences (KFDX: No. 2024-1037)
Chemicals, peptides, and recombinant proteins		
Liquid metal (Ga, In, Sn)	Non-ferrous Metal Co.	high-purity (99.99%)
Sodium chloride	Sinopharm	R019772, CAS: 7647-14-5
Software and algorithms		
Origin 2021	Origin	https://www.originlab.com/2021
ChemDraw Professional 18.0	PerkinElmer	https://www.perkinelmer.com/category/chemdraw
Endnote X8	Endnote	https://support.clarivate.com/Endnote/s/article/Download-EndNote?language=en_US

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Materials

Eutectic liquid-metal alloys, specifically Gallium-Indium-Tin (GaInSn) with a composition of 68.5% Gallium, 21.5% Indium, and 10% Tin by mass, and Eutectic Gallium-Indium (GaIn) with a composition of 75% Gallium and 25% Indium by mass, were synthesized from high-purity (99.99%) elemental Gallium, Indium, and Tin. These constituents were introduced into a beaker in their respective mass ratios and subjected to a thermal treatment at 100°C to ensure the formation of a homogeneous alloy mixture, which was subsequently employed in the experimental procedures. Normal saline (0.9% sodium chloride) was prepared using sodium chloride. Blood was collected from patients at partner hospitals. All procedures were approved by the Ethics Committee of University of Health and Rehabilitation Sciences (KFDX: No. 2024-1037), Qingdao, China. Deionized water (Milli-Q System, Millipore, USA) was used in the experiments.

METHOD DETAILS

Characterization

Blood routine examination was tested by blood routine analyzer (Sysmex XS-800i) in Affiliated Hospital. And biochemical index was monitored by biochemical analyzer (Beckman, Counter, AU2700) in Affiliated Hospital. The surface morphology of the liquid metals (LMs) was analyzed pre- and post-incorporation into blood or serum using a field-emission scanning electron microscope (FESEM, JSM-7100F, JEOL). Elemental composition was determined by energy dispersive spectrometer (EDS). Chemical bonding was further assessed through Fourier transform infrared (FT-IR, CARY670, Agilent) spectroscopy within the wave-number range of 4000 to 500 cm^{-1}. And liquid metals in pure water and normal saline (0.9% sodium chloride) were designed as control groups.

Composition test in blood/serum

In order to research the effect of gallium-based liquid metals on components in blood or serum, Ga, GaIn and GaInSn were used as the representative liquid metals in the whole test. In detail, firstly 1 mL bulk Ga, GaIn, GaInSn was added into each blood group, respectively. The blood without liquid metal is used as the blank group. Then, after a certain amount of time (0 h, 2 h, 5 h, 7 h), analysis of components in the blood was used by blood routine analyzer (Sysmex XS-800i). For biochemical index, the blood was centrifuged with 3000 rpm to obtain the serum, then was monitored by biochemical analyzer (Beckman, Counter, AU2700).

QUANTIFICATION AND STATISTICAL ANALYSIS

Data were analyzed with origin 2021 (Origin Software). The molecular formula is drawn by ChemDraw Professional 18.0. All human blood and serum were used in the *in vitro* experiments. N represents the number of blood samples. One-way ANOVA was used to study differences between blood samples with different contact time of liquid metals and control group without liquid metals. Significance was determined at $p < 0.05$. All statistical analyses were performed with origin 2021.