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Review Article

Recent Progress and Future Direction for the Application of Multiomics Data in Clinical Liver Transplantation

Zhengtao Liu[1,2,3,4#], Jun Xu[2#], Shuping Que[5], Lei Geng[2], Lin Zhou[3,4], Adil Mardinoglu[6,7*] and Shusen Zheng[1,2,3,4*]

[1]Shulan International Medical College, Zhejiang Shuren University, Hangzhou, Zhejiang, China; [2]Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China; [3]NHC Key Laboratory of Combined Multi-organ Transplantation, Key Laboratory of the diagnosis and treatment of organ Transplantation, CAMS, First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China; [4]Key Laboratory of Organ Transplantation, Zhejiang Province, First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China; [5]DingXiang Clinics, Hangzhou, Zhejiang, China; [6]Science for Life Laboratory, KTH-Royal Institute of Technology, Stockholm, Sweden; [7]Centre for Host-Microbiome Interactions, Faculty of Dentistry, Oral & Craniofacial Sciences, King's College London, London, UK

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Abstract

Omics data address key issues in liver transplantation (LT) as the most effective therapeutic means for end-stage liver disease. The purpose of this study was to review the current application and future direction for omics in LT. We reviewed the use of multiomics to elucidate the pathogenesis leading to LT and prognostication. Future directions with respect to the use of omics in LT are also described based on perspectives of surgeons with experience in omics. Significant molecules were identified and summarized based on omics, with a focus on post-transplant liver fibrosis, early allograft dysfunction, tumor recurrence, and graft failure. We emphasized the importance omics for clinicians who perform LTs and prioritized the directions that should be established. We also outlined the ideal workflow for omics in LT. In step with advances in technology, the quality of omics data can be guaranteed using an improved algorithm at a lower price. Concerns should be addressed on the translational value of omics for better therapeutic effects in patients undergoing LT.

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Keywords: Multiomic analysis; Transcriptomics; Proteomics; Metabolomics; Liver transplantation; EAD.

Abbreviations: AFP, alpha-fetoprotein; AI, artificial intelligence; CHC, chronic hepatitis C; CIT, cold ischemia time; DCD, donors after cardiac death; EAD, early allograft dysfunction; GEO, Gene Expression Omnibus; GF, graft failure; GTEx, Genotype-Tissue Expression; HCC, hepatocellular carcinoma; IPF, initial liver function; IRI, ischemic reperfusion injury; Lasso, Least absolute shrinkage and selection operator; LC-MS, liquid chromatography-mass spectrometry; LDLT, living donor liver transplantation; LT, liver transplantation; MaS, macrosteatosis; PNF, primary nonfunction; TCGA, The Cancer Genome Atlas; WGCNA, Weighted gene coexpression network analysis.

[#]Contributed equally to this work.

[*]**Correspondence to:** Adil Mardinoglu, Science for Life Laboratory, KTH-Royal Institute of Technology, Stockholm, Sweden. ORCID: https://orcid.org/0000-0002-4254-6090. Tel: +46-31-772-3140, Fax: +46-31-772-3801, E-mail: adilm@scilifelab.se; Shusen Zheng, Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang 310003, China. ORCID: https://orcid.org/0000-0003-1459-8261. Tel/Fax: +86-571-87236570, E-mail: shusenzheng@zju.edu.cn

Introduction

As one of the most common causes of death, liver disease severely impairs global health and utilizes abundant health resources in countries worldwide.[1] Currently, liver transplantation (LT) is one of the most effective therapeutic approaches for the treatment of end-stage liver disease and acute hepatic failure;[2,3] however, the therapeutic effects of LT are not equal among patients and the prognosis of recipients is determined by many factors related to recipients, donors, grafts, surgery, and post-operative treatment.[4] In addition, donor-recipient matching is also essential for improving LT quality.[5] LT involves systematic engineering that requires cooperation from the medical staff, scientists, engineers, technicians, and patients. The optimal procedure for LT should be developed on the premise of comprehensive collection of information from each step to maximally benefit the patients. Omics data from the donor, recipient, and graft samples can provide potential approaches to depict the panorama of the working environment for "new organs" in the body. Critical biomarkers might facilitate better organ allocation for most suitable patients.[6] Indeed, well-organized clinical cohort studies with inclusion of multiomics data can provide an inspiration for better organ utilization and mechanistic studies.

Omics is the suffix applied to a series of disciplines in the science and medicine domains to acquire systems knowledge on the collective characteristics of molecules from the entire genome, transcriptome, proteome, metabolome, and microbiome. Moreover, studies involving whole molecules from subspecies, such as the lipidome or glycome, are also attributed to the domain of omics.[7,8] Omics data describe the dynamic variations of molecules from a macroscopic

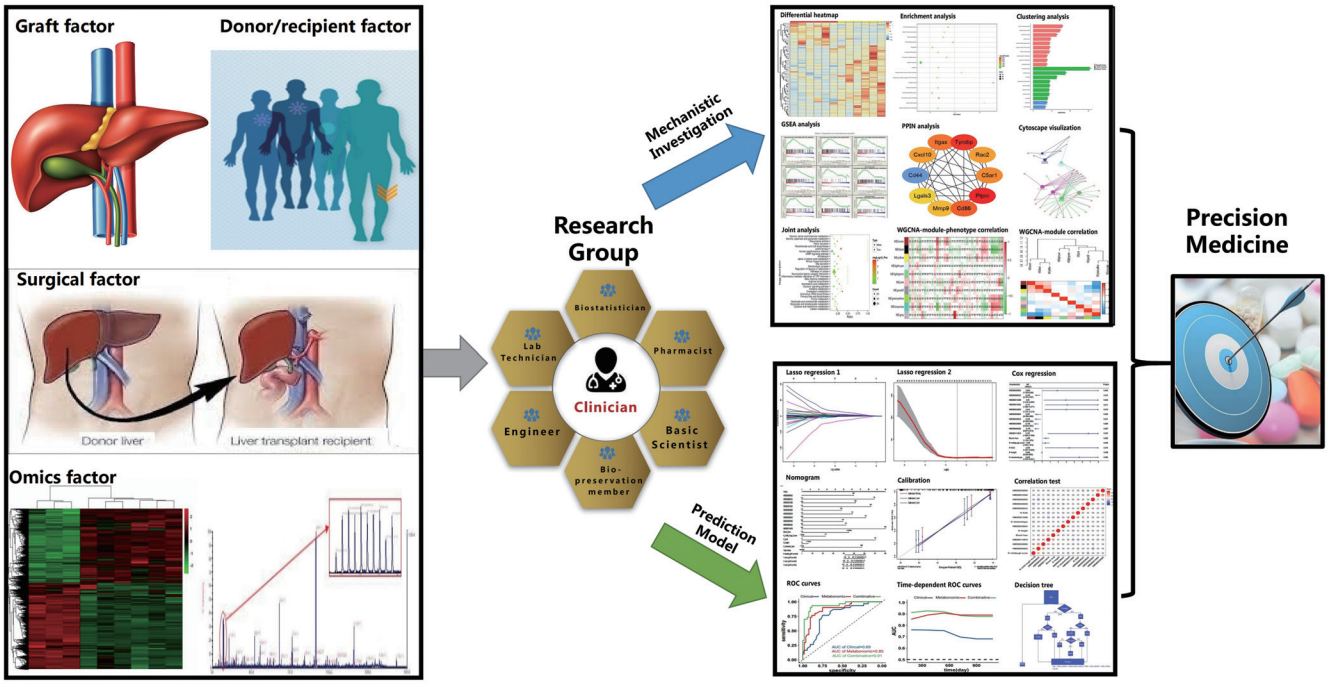

Fig. 1. Research strategy for individualized treatment of key issues in LT based on multiomics clinical data. LT, liver transplantation.

perspective, which might help researchers to screen and thoroughly evaluate candidates. Moreover, integrative multiomics studies have also shown the advantages of a better understanding of the molecular function and investigation of disease prediction with mutual validations at all levels.[9,10]

Following improvements in assay technology and statistical algorithms, an increasing number of omics-based studies have been devoted to clinical investigations for comprehensive considerations with lower prices than ever before.[11] Criteria from authoritative institutions have been legislated to guarantee the high-quality and provide guidance on further clinical trials;[12,13] however, unlike laboratory models, enormous heterogeneities have been observed in human phenotypes and the panel of disease features has been defined with a specific terminology ("phenomics").[14] Clinical omics studies aim to demonstrate the inner mechanism of complex phenotypes based on a comprehensive consideration of whole molecule profiles in patients with common features, such as disease and therapy, by construction of a network model from omics data. The objective of clinical omics studies can be summarized into two parts, as follows: 1. identify the key targets for better individualized treatment of patients for disease prevention, diagnosis, therapy, prognostication, and response to medication; and 2. provide inspiration for further mechanistic investigations involving the key features of disease based on the mathematical relationships of basic science.[7,15,16] Currently, more and more large sample-based clinical omics data with a focus on different types of patients have been published and deposited in public databases, such as Gene Expression Omnibus (GEO), The Cancer Genome Atlas (TCGA), and Genotype-Tissue Expression (GTEx).[17–19] These databases provide potential approaches for researchers to initiate additional "omics-wide" investigations of their interests through free data mining via ready-made, bio-informatic workflows.[20] Otherwise, well-organized trials with assays of self-prepared omics data from specific samples in patients with relatively rare diseases or treatments are also worthy of mechanistic investigation and individualized therapy. Additionally, integrative software packages, on-line toolkits, and workflows were developed to lower the barriers for analysis, exploration, and explanation of omics data, and the potential for clinical utilization.[21,22] Indeed, increased participation by experienced clinicians with critical thinking and clinical reasoning in omics research as a carrier of multidiscipline cooperation by physicians, bioinformaticians, biologists, and engineers might help to substantially improve the quality of clinical omics studies.[23]

Surgery is usually aimed at the treatment of severe disease, such as cancer, at the expense of resecting partial or entire organs. In contrast, transplantation medicine was a new surgical field in which an exhausted organ was replaced by a new organ from another person with a completely alien genetic background.[2,24] More complexity was presented for various potential genetic confounders linked to the donors and recipients involved in the LT process with an impact on surgical quality and post-operative outcomes.[25,26]

As a crucial tool for improving the quality of clinical LT, the widely used omics analysis provides an approach to acquire systematic knowledge that facilitates construction of the genetic architecture and clarification on the impacts on prognosis (including mortality or cellular rejection) of patients after LT, which might help to improve the treatment of key issues, such as graft selection and donor-recipient matching.[6,27–34] Otherwise, the molecular mechanisms underlying key issues, such as ischemic reperfusion injury (IRI) and operational tolerance in LT were also discussed in a previous multiomics study.[35–39] A variety of omics studies involving solid organ transplantation have been collectively named transplantomics as a potential approach for the individualized treatment of transplant patients (Fig. 1).[40,41]

Despite the number of studies that have been published, the application of omics data for clinical LT is rarely summarized.[31,37–39,42–45] Based on our previous study, the major peri-operative risk factors for LT were divided into four categories (including recipients, donors, grafts, and surgery).[39,46] We summarized the prior achievements of clinical omics studies that were categorized according to the above-

mentioned factors. More importantly, future directions on the application of omics with positive benefits for patients who underwent LT operations were highlighted based on the perspectives of experienced surgeons.

Current application of omics data in clinical LT investigations

Studies including less than 15 LT cases were excluded for guarantee of data reliability. Studies aimed at the selection of potential molecular targets under an unsupervised model were reviewed and categorized based on sample species (tissues, peripheral sera/plasma from donor, recipient, or graft).

As presented in Tables 1 and 2, a total of eight studies have reported the connections between omics data and phenotypes in clinical LT.[31,37–39,42–45] Metabolomics is the most-used assay involved in all omics studies. Most researchers prefer to collect samples from graft tissues and omics data from recipient sera, but such were only assayed in three studies. As a common short-term complication, early allograft dysfunction (EAD) was the focus in most studies. In addition, post-transplant fibrosis, graft failure, tumor recurrence, and marginal organs were also discussed in select studies. Crossomics analysis and data integration were only performed in one study, with non-identical sample origins.[42] More details were introduced by sample species, as discussed below.

Omics data for assessing organ function after LT

Four studies, all of which involved European cases,[37,38,43,45] predesignated EAD as a major post-transplant outcome by mass spectrometry using a similar comparison strategy. After reanalysis of prominently expressed potential metabolites from published studies, we showed that the glycerophospholipid, histidine, and purine metabolism pathways had significant deviations in EAD cases (Fig. 2). It is noteworthy that dysfunctional glycerophospholipid metabolism was also shown to be a major cause of macrosteatosis (MaS) and graft failure (GF) in a prior study from our center.[39] We speculated that a derangement in glycerophospholipid might be a link to inferior organ quality, such as MaS, to early graft dysfunction and final organ failure in LT.

Omics data for assessing primary disease recurrence

The predictive value of noninvasive biomarkers from recipient sera was evaluated in cohorts with a specific etiology (hepatocellular carcinoma [HCC] or chronic hepatitis C [CHC]) from three studies.[31,42,44] Among LT recipients with chronic hepatitis C, post-transplant fibrotic severity can be differentiated based on metabolite clusters, including sphingomyelins and phosphatidylcholines. Severe liver fibrosis can be followed by down-regulation on glutathione biosynthesis. Oxidative stress might be involved in regulating fibrogenesis after LT.[31,42] Our metabolomic data in plasma samples from pretransplant HCC patients also showed the combined application of classical biological biomarkers, such as alpha-fetoprotein (AFP), phosphatidylcholine, and nutriacholic acid, might improve the predictive accuracy of tumor recurrence.[44] Additional details are presented in Table 2.

Limitations of current LT-related omics studies

Collectively, current omics data involving LT are scattered, with a lack of a systematic framework and validation testing. Most LT-related omics studies have adopted a retrospective design pattern. Because of the lower price and easy-to-conduct workflow, liquid chromatography-mass spectrometry (LC-MS) is the most commonly used tool for metabolomic assays. Other platforms, such as next-generation sequencing (NGS) and even multiomics studies with mutual validation in a fixed cohort are urgently needed in future LT-related omics studies.

Despite the importance of donor risk on post-transplant outcomes mentioned in previous studies,[47,48] we found no reported omics data from donor blood samples to represent the general donor condition and the impact on LT quality. Donor features can be easily regulated as a flexible indicator by short-term intervention on exercise, diet, and drugs. These effects were more apparent in living donor liver transplantation (LDLT).[49] The knowledge gap in omics data from donor sera should be filled by future studies, which might lead to novel findings of manageable targets to improve LT quality.

Future directions for omics studies in LT

Many omics studies involved in the process of clinical LT have been conducted over the past decades. The profiles for proteomes and metabolomes from biological samples in the peritransplant period were outlined to determine the interested issues in LT cases from an omics perspective. Key molecules and pathways involved in transcriptomics might provide potential targets for further translational studies.[40,41]

Despite these advances, limitations and many gaps still exist among the literature for clinical LT studies. Specifically, these limitations can be summarized as follows: 1. fewer multiomics studies with the inclusion of multi-dimensional samples (tissues and sera) in a fixed LT cohort; 2. lack of donor-recipient-matched omics data to show the panorama of LT; 3. lack of dynamic and longitudinal omics data to show the tendency of key molecules before and after LT; 4. insufficient participation of more advanced technologies, such as single-cell RNA sequencing; and 5. lack of deep data-mining by construction of networks with clinical and omics factors. These limitations might affect the translational value of omics data in LT research. Transplantation is the crown in all liver surgical operations. Omics studies are urgently needed to guide clinical LT to maximize the benefits to patients worldwide.[50] In contrast, LT is a far more complex systematic engineering process affected by many factors from clinical, environmental, and the genetics of the donor and recipient.[6,51–53] Therefore, omics projects in LT need cooperative networks of clinicians, pharmacists, bioinformaticians, and biologists, with comprehensive consideration of the abovementioned potential factors in an appropriate algorithmic model. Thus, actions with considerate concerns on abovementioned factors are warranted in omics studies for LT cases.

Analysis of multiomics and multidimensional systems in LT cases

Undoubtedly, the multiomics analysis which combines data from various high-throughput technologies has provided meaningful approaches to better understand molecular mechanisms and construct predictive models.[54–57] Data from our center indicated a high efficiency of integrative omics assays on the prediction of tumor burden in liver cancer patients.[58] However, multiomics data of high quality were rarely reported in prior clinical investigations on LT cases.

Table 1. Literature features with original reports of clinical omics for LT

Author, Country, Publication year [Reference]	Case number, Indication for LT, Donation type	Sampling time, Follow-up duration	Sample species, Comparison	Platform	Major findings
Diamond, USA, 2012[42]	15, CHC, NA	2003–2004, 12 months	Graft tissue, Fibrosis (F3-F4 vs. F0-F2)	MS, Proteomics	Oxidative stress in rapid fibrosis progression observed in CHC recipients
	60, CHC, NA	2004–2005	Recipient serum, Fibrosis (F3-F4 vs. F0-F2)	LC-MS, Metabolomics	
Cortes, Spain, 2014[38]	123, NA, DBD	2009–2012, 2 weeks	Graft tissue, EAD vs. IGF	LC-MS, Metabolomics	Metabolomic factors facilitate decision making on accepting or rejecting an organ to improve donor allocation
Xu, UK, 2015[43]	56, NA, DBD (38)/ DCD (18)	NA, 2 weeks	Graft tissue, EAD vs. IGF	LC-MS, Lipidomics	LysoPC (16:0) and LysoPC (18:0) might be involved in signaling transduction in liver tissue damage due to warm ischemia before transplantation
Faitot, France, 2017[37]	42, Mixed, NA	2014–2016, 2 weeks	Graft tissue, EAD vs. Non-EAD	NMR, Metabolomics	Metabolites showed lactate >8.3 mmol/g and phosphocholine >0.646 mmol/g were significantly associated with graft dysfunction with excellent accuracy
Cano, Spain, 2017[31]	203, CHC, NA	NA, 1 year	Recipient serum, Fibrosis (F3-F4 vs. F0-F2)	LC-MS, Metabolomics	An algorithm consisting of two sphingomyelins and two phosphatidyl cholines accurately classified rapid and slow fibrosers after transplantation with AUROC on 0.92
Lu, China, 2019[44]	199, HCC, DCD	2012–2016, 2 years	Recipient serum, HCC recurrence (HCC vs. LC+HC)	LC-MS, Metabolomics	PC (16:0/P-18:1), PC (18:2/ OH-16:0), nutriacholic acid were independently related to tumor recurrence with high efficiency to predict HCC recurrence
Xu, UK, 2020[45]	47, NA, DBD (27)/ DCD (20)	2011–2014, followed till 2019	Graft tissue, EAD vs. EGF	LC-MS, Metabolomics	Combination of AMP/urate, adenine/ urate, hypoxanthine/urate and ALT proved to have higher prediction ability on EAD compared to a combination of conventional liver function and risk markers
Liu, China, 2020[39]	82, Mixed, DBD (22)/DBCD (14)/ DCD (46)	2015–2019, 616 days	Graft tissue, GF vs. non-GF/ MaS vs. non-MaS	LC-MS, Metabolomics	Dysfunction on glycerophospholipid Metabolism linked the incidence of donor MaS and GF; decrements on PC and PE amplified the fatal effects of MaS on organ failure

AUROC, area under the receiver operating characteristic curve; CHC, chronic hepatitis C; DBCD, donation after brain and cardiac death; DBD, donation after brain death; DCD, donation after cardiac death; EAD, early allograft dysfunction; GF, graft failure; HC, healthy control; HCC, hepatocellular carcinoma; HR-MAS NMR, high-resolution magic-angle-spinning nuclear magnetic resonance; IGF, immediate graft function; IQR, interquartile range; LC, liver cirrhosis; LC-MS, liquid chromatography coupled to mass spectrometry; MaS, macrosteatosis; NA, not available; PC, phosphatidylcholine; PE, phosphatidylethanolamine.

Table 2. Key mechanisms referred in enrolled clinical omics studies

Name, Publication year [Ref]	Comparison, sample, assay	Key molecule	Key pathway
Diamond, 2012[42]	F3-F4 vs. F0-F2 fibrosis, graft tissue, proteomics	PRKAR2A, TCERG1, DGCR8, WBSCR22, MYH11, PCBP1, GSTK1, TPM1, PFDN1, CDC42	UP: CTLA4 signaling in cytotoxic T lymphocytes, cytotoxic T lymphocyte–mediated apoptosis of target cells, Allograft rejection signaling, OX40 signaling pathway, graft-versus-host disease signaling
			DN: Arylhydrocarbon receptor signaling, glutathione metabolism, Metabolism of xenobiotics by cytochrome P450, NRF2-mediated oxidative stress response, xenobiotic metabolism signaling
	F3-F4 vs. F0-F2 fibrosis, recipient serum, metabolomics	UP: methionine, serine, gamma- glutamylglutamate, gamma- glutamylphenylalanine	
		DN: Cysteine	DN: Glutathione biosynthesis
Cortes, 2014[38]	EAD vs. IGF, graft tissue, metabolomics	NA	UP: Phospholipid degradation, histidine metabolism, bile acids biosynthesis
			ALTERED: Ammonia recycling, urea cycle
Xu, 2015[43]	EAD vs. IGF, graft tissue, lipidomics	LysoPC (16:0), LysoPC (18:0)	NA
Faitot, 2017[37]	EAD vs. Non-EAD, graft tissue, metabolomics	Lactate, phosphocholine	NA
Xu, 2020[45]	EAD vs. EGF, graft tissue, metabolomics	AMP, urate, adenine	Purine metabolism
Liu, 2020[39]	GF vs. non-GF, graft tissue, metabolomics	Calcidiol, delta7-avenasterol, presqualene diphosphate, episterol, 5-dehydroepisterol, 4,4-dimethylcholesta-8,14,24-trienol	Steroid biosynthesis
	MaS vs. non-MaS, graft tissue, metabolomics	PC (20:5/16:0), linoleic acid, PE (20:4/22:6), PE (20:5/18:2), LysoPC (20:3), LysoPC (20:4), LysoPC (22:4), LysoPC (22:5), phosphocholine, 1-phosphatidyl-D-myo-inositol	Linoleic acid, glycerophospholipid metabolism
	Overlapped MaS+GF		Glycerophospholipid metabolism

DN, downregulated; EAD, early allograft dysfunction; GF, graft failure; IGF, immediate graft function; MaS,macrosteatosis; UP, upregulated.

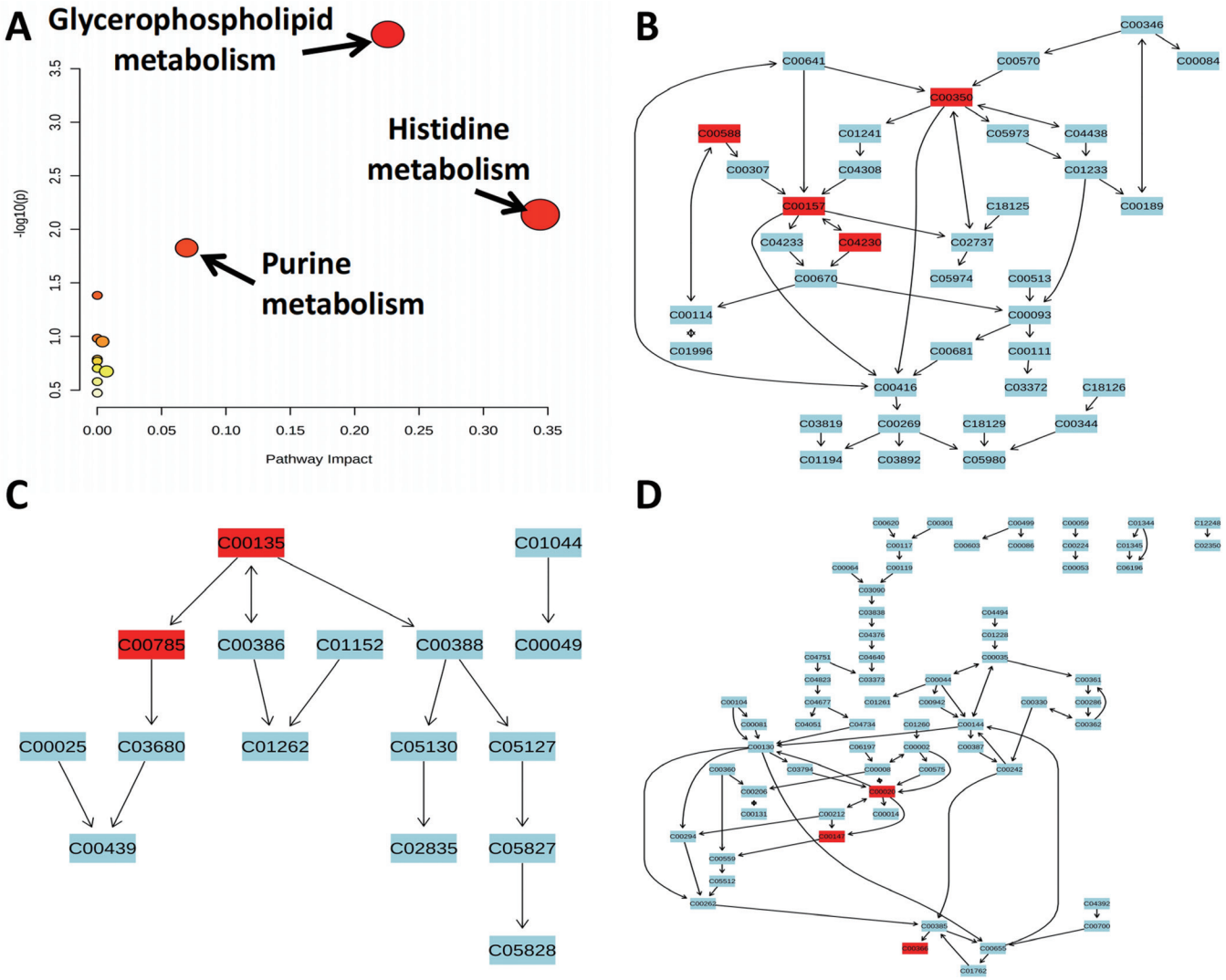

Fig. 2. Reanalysis of positive metabolites that associated with EAD in prior metabolomic studies. (A) Pathway analysis based on positive metabolites associated with EAD occurrence in prior metabolomic studies. (B) Details of pathway on glycerophospholipid metabolism and positive metabolites associated with EAD. (C) Details of pathway on histidine metabolism and positive metabolites associated with EAD. (D) Details of pathway on purine metabolism and positive metabolites associated with EAD. EAD, early allograft dysfunction.

As discussed in our prior review (part II), clinicians tend to use metabolomic assays to explore the potential mechanisms underlying key issues in LT. The possible explanation might be due to the low quality of samples with severe RNA degradation after removal from donor bodies.[59,60] A previous study reported that the intactness of tissues from different organs was inconsistent following the same cold ischemia exposure after surgical resection.[61] With respect to the liver, the RNA appears to tolerate long-distance transportation with grafts from donors after cardiac death (DCD). In a cohort of grafts from cadaveric LT, our ongoing project showed that >93% of graft tissues (41 of 44 samples) were suitable for further RNA-seq analysis even through long-term cold ischemia time (CIT). The prerequisites for RNA-seq analysis were as follows: 1. sample freshness and RNA extraction within 3 months; 2. shortened duration between the end of CIT and snap-freezing in liquid nitrogen (<30 m); and 3. avoidance of repeated freezing and thawing (<2 times). Data from our study indicated the feasibility of transcriptomics assays in liver grafts from a citizen-based organ donation system (Fig. 3). Projects with well-designed RNA-seq are desirable in further LT studies.

With the exception of solid organ tissues, omics data from biological fluids, such as peripheral blood, also showed advantages in disease screening and biomarker investigation in LT.[62] Specifically, the superiority of omics studies on blood samples is realized in noninvasive and repeated sampling,[6] and these features support blood omics as an appropriate tool in dynamic monitoring programs, such as graft rejection, drug responses, and operational tolerance in LT.[63,64] An algorithm was developed to predict post-transplant acute rejections by gene expression arrays in USA-based patients.[62] Data from our center also confirmed the potential availability of the metabolomics assays on peripheral blood samples for prognostication of patients who underwent LT.[44] In spite of the limitations (instability and internal/external heterogeneity) for omics results in blood samples,[6] the diversity of omics assays (transcriptomics, proteomics, and metabolomics), and paralleled multi-sample dimensions (tissues/sera from donors/recipients) within

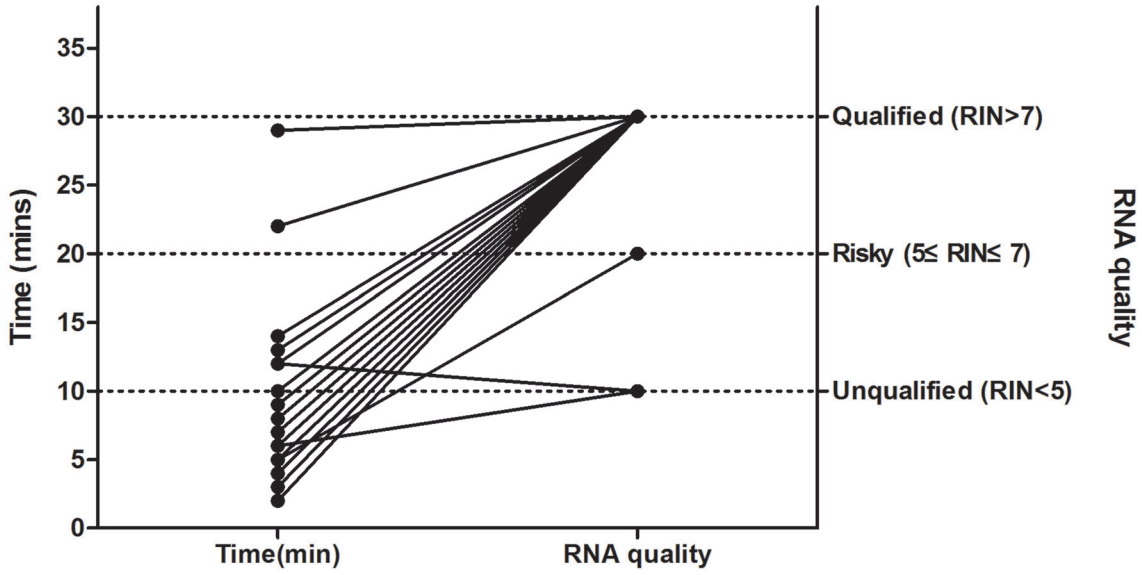

Fig. 3. Matched scatter plot between sample snap freezing time* and RNA quality for transcriptomic analysis. *Snap-freezing time indicates the period between the end of cold preservation and snap-freezing in liquid nitrogen. Correlation analysis was performed by Spearman's test. Insignificant correlation was observed between snap-freezing time and RNA quality.

the same LT cases is recommended and might provide possible approaches to better uncover the potential biomarkers for individualized treatments of problems occurring in the peritransplant process.

Importance of donor-recipient-matched omics data in clinical transplantation

The importance of donor-recipient-matched genetic heritage has been emphasized in previous studies; however, the availability of relevant data was limited due to their low throughput with inclusion of single-to-several genes or genetic polymorphisms.[25,65,66] Omics data provide available approaches to understand the entire genetic background of LT donors and recipients, which might facilitate the development of potential therapeutic targets and better management of LT patients. The effect of donor features might be conditionally exerted on recipient features and vice versa. Therefore, an individually-matched omics study with considerations of the recipient and donor will provide evidence with more reliability and persuasion for precise treatment of LT cases.[40,67,68] A challenge is also anticipated in assessing the synergistic effects using an appropriate mathematical model. Key issues in the LT process are influenced by a network of factors from the recipient, donor, surgery, and post-transplant immunotherapy, with various internal and external connections.[69] Advanced statistical methodologies with dimensional reductions are necessary in LT studies with the inclusion of integrative high-throughput data.[70] Weighted gene coexpression network analysis (WGCNA) is strongly recommended for dimensional reduction to build the connections between omics and clinical traits in LT cases.[71] In the matrix of the WGCNA algorithm, omics traits can be clustered into differentiated modules. The mathematical connections between clinical traits in LT, such as primary nonfunction (PNF) or EAD and modules might help for further investigate the inner mechanism of these phenotypes in the LT process. Least absolute shrinkage and selection operator (Lasso) regression is another option in omics studies and key molecules can be screened out by Lasso regression for scale reduction.[72,73] More details are shown in Figure 4.

In addition, the involvement of artificial intelligence (AI) and machine learning algorithms might also provide integrative analyses of high-throughput datasets.[74–76]

Necessity of dynamic and longitudinal omics studies in LT cases

Many phenotypes, such as drug response, might vary across different stages during the entire disease process. Dynamic omics data might help to uncover the mechanisms underlying this development.[77,78] Similarly, longitudinal omics data [e.g., before/after cellular rejection] might also help biomarker development and allograft monitoring in LT cases.[28] Continuous metabolomics assays on sera samples from recipients were also performed to build the link between metabolite profiles and post-transplant outcomes.[34]

Researchers tend to conduct dynamic omics by utilizing biological fluid samples for the simplicity of repeated sampling; however, the projects with dynamic omics results are far less often reported than needed in LT. Using graft steatosis as an example, the reversal of graft steatosis was observed in most cases of grafts used for LT; such reversal might have benefits on prolonged post-transplant survival.[79,80] Additionally, we found that reversed fat deposition partially determined the fate (i.e. survival or death) of recipient rats after LT.[81] Multiomics studies with a focus on dynamic changes of histologic steatosis *in vivo* might elucidate this mechanism and potential biomarkers. Collectively, longitudinal omics data are worthy, in some circumstances, to fill in the knowledge gap for precise treatment in clinical LT.

Validation of transplantomics studies

The validity of multiomics results should be ensured based on validation practices over multiple steps.[12] The importance of validation for omics studies for LT research has also been mentioned in a previous report.[6] The validity of data

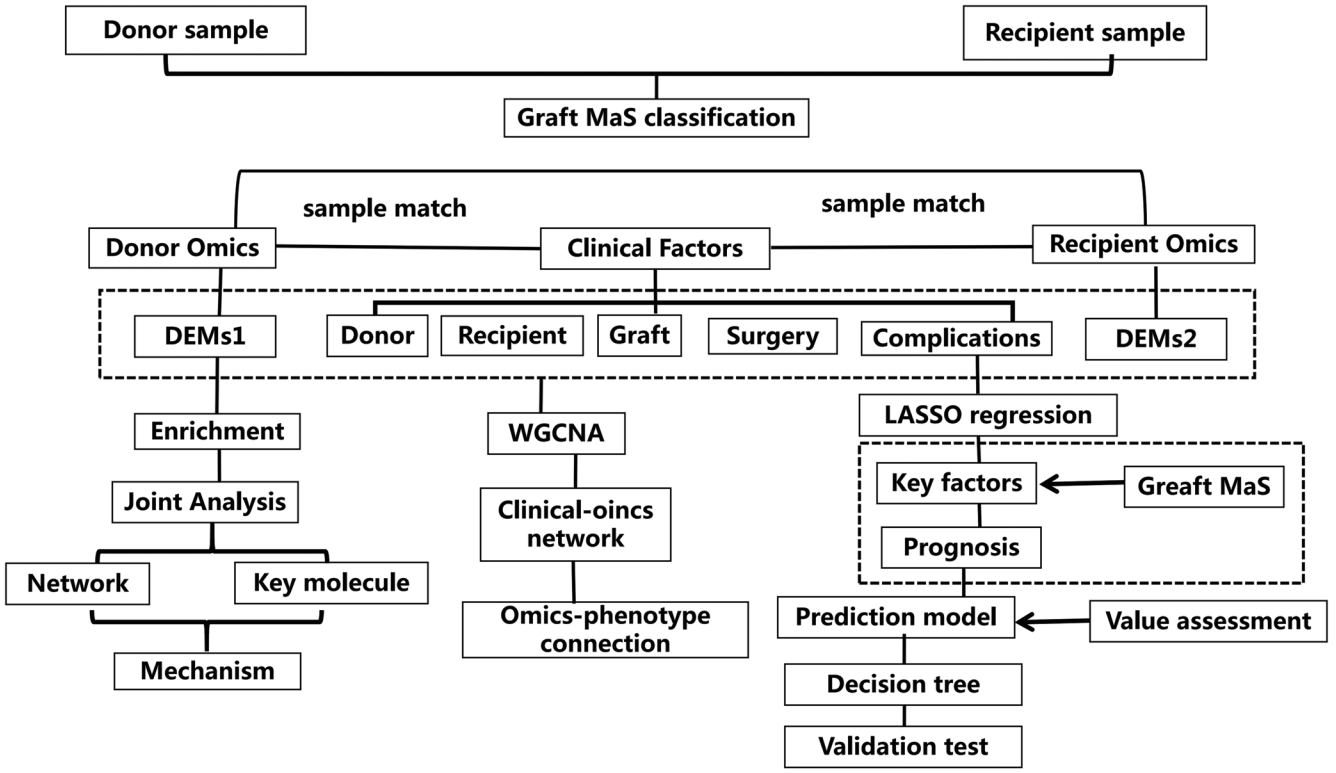

Fig. 4. Recommended flowchart for multiomics study in LT cases. LT, liver transplantation.

is routinely tested via internal or external validation. Multicenter omics studies, including validation from relatively independent patient cohorts, yield more reliable biomarker panels in predicting post-transplant rejection with higher translational value.[62] With the technologic development of omics assays, the cost of a commercial omics kit is lower with complete and individualized analytic platforms. Differentiated with typical design referred in previous literature,[12] new concepts should be imported in omics validation in LT studies.

First, potential mechanisms can be verified by mutual validations across multiomics data. Candidate molecules from transcriptomics, proteomics, and metabolomics can be simultaneously mapped in the KEGG database, and can be strengthened by joint omics studies.[82] Furthermore, omics validation in model organisms, such as cell lines or rats, might also help to distinguish the roles of omics molecules on key issues in LT. Biases are inevitable for disturbance from confounders in clinical transplant-related studies.[83] Integrative omics studies from patients and model organisms with preset targets might help better understand the underlying mechanisms. Therefore, validation in a LT study does not only simply mean an enlarged sample size. We applied more updates via measures on omics assays for the better treatment of LT cases.

Utilization of online platforms for statistics in multiomics studies

Currently, many online tools have been developed for the integration of omics data.[84] Usually, a web-based tool has a user-friendly interface with a programmable procedure to run the data using pres*et al*gorithms. With the help of these online platforms, a shortened study curve was presented to researchers regarding omics data analysis.[85–87] As an example, MetaboAnalyst (https://www.metaboanalyst.ca/) is a popular online tool that analyzes metabolomics and multiomics data.[88] The website provides online services with coverage from basic statistics, such as quantitative comparisons and principal component analysis, to advanced clustering, enrichment, and pathway analysis. It is noteworthy that joint multiomics analyses can be conducted and visualized in MetaboAnalyst with an entire set of R codes for the retrospective evaluation of potential errors.

More and more online resources have been developed to deal with multiomics data via ready-made sets of protocols prepared by statisticians that promote the translational value of omics results for clinical LT.[84,89] Technological issues should not be barriers of clinical LT studies. User-friendly and open access online platforms have been developed by biostatisticians with mature protocols for the treatment of omics data. Clinicians should pay more attention to the association between omics data and clinical traits. In contrast, timely updates on platforms are also needed to adapt to the rapid technological upgrade in omics assays.

Importance of contributions from experienced clinicians

We have come into the omics era, and it has been followed by technological development. Lower unit prices guarantee the feasibility of multiomics studies in clinical LT cases; however, lower costs also cause abuse of omics studies. Low-quality omics studies might produce redundant information to confuse decision-making in LT.[90,91] In our opinion, the academic value of omics studies rely on the ability to improve LT therapeutic efficiency. Thus, investment in omics test resources should uncover key traits with signifi-

cant potential to improve clinical LT quality. The increasing participation of experienced clinicians can also help to express the clinical requests of omics studies.[23] A reliable and replicable clinical trait with translational potential is a good beginning for clinical omics studies in LT.

Using MaS grafts as an example, we found inferior prognoses in patients who received MaS organs with poor concurrent initial liver function (IPF) after LT (a phenomenon with clinical significance).[46] The validity of this connection was demonstrated in another cohort with similar features (i.e. replicability). A metabolomics assay was performed to investigate the mechanism and biomarker for machine perfusion to improve the quality of marginal grafts (i.e. translational potential).[39] Further omics studies are ongoing in a rat LT model (i.e. laboratory investigation),[81] and collectively, clinicians are responsible for playing a central role in implementing a meaningful project with the goal of better treatments for LT patients. In contrast, clinical omics in LT also require a well-organized consortium with a cooperative network of pharmacists, bioinfomaticians, scientists, and technicians.

Ideal flowchart for multiomics studies in LT cases

Based on the points discussed above, we suggest that a well-designed omics study in LT should be based on the following: 1. prospective destination with adequate sample storage; and 2. a research topic with adequate translational value. The molecular mechanism of MaS organs on post-transplant prognosis was detailed in our previous study.[39] The details of the recommended flowchart are presented in Figure 4. Specifically, omics data (transcriptomics, proteomics, or metabolomics) can be procured from samples (tissues/sera) from the donor and recipient, and classified by graft's MaS status. First, the mechanism underlying organ MaS on post-transplant outcomes can be deduced by joint omics analysis. Then, WGCNA can be performed to construct the network and evaluate the clinical omics connection, and the impact on post-transplant outcomes. Third, omics data can be used in the construction of a MaS-related prediction model on post-transplant prognosis. It is noteworthy that the complex omics result is complicated and does not provide a clear expression to readers and in data visualization by tools, such as Cytoscape (https://cytoscape.org/), MetaboAnalyst, and other platforms, might help to highlight the key results.[92]

Conclusions

In conclusion, this review retrospectively evaluated the application of multiomics studies on clinical LT in the past decades and assessed the translational values on mechanistic investigations and therapeutic aims. We forecasted the future directions for omics studies in clinical LT and called for more participation by clinicians in the cooperative consortium. Finally, we shared the flowchart for the use of multiomics data on clinical LT cases. In the coming omics era, the quality of omics data can be guaranteed by improved algorithms with a lower cost, followed by technological development. More mention should be raised on the translational value of further mechanistic exploration and better treatment of LT cases.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conception and design of the study (ZL and SZ), data extraction (JX), data analysis (SQ), drafting of the manuscript (ZL, JX), and review of the manuscript for important intellectual content (LG, LZ, AM, SZ). All of authors approved the final version of manuscript for submission.

Data sharing statement

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

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