Original Article

# Clinical studies of magnetic resonance elastography from 1995 to 2021: Scientometric and visualization analysis based on CiteSpace

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**Background:** To assess the knowledge framework around magnetic resonance elastography (MRE) and to explore MRE research hotspots and emerging trends.

**Methods:** The Science Citation Index Expanded of the Web of Science Core Collection was searched on 22 October 2021 for MRE-related studies published between 1995 and 2021. Excel 2016 and CiteSpace V (version 5.8.R3) were used to analyze the downloaded data.

**Results:** In all, 1,236 articles published by 726 authors from 540 institutions in 40 countries were included in this study. The top 10 authors published 57.6% of all included articles. The 3 most productive countries were the USA (n=631), Germany (n=202), and France (n=134), and the 3 most productive institutions were the Mayo Clinic (n=240), Charité (n=131), and the University of Illinois (n=56). The USA and the Mayo Clinic had the highest betweenness centrality among countries and institutions, respectively, and played an important role in the field of MRE. In this study, the 24,347 distinct references were clustered into 48 categories via reasonable clustering using specific keywords, forming the knowledge framework. Among the 294 co-occurring keywords, "hepatic fibrosis", "stiffness", "skeletal muscle", "acoustic strain wave", "in vivo", and "non-invasive assessment" were research hotspots. "Diagnostic performance", "diagnostic accuracy", "hepatic steatosis", "chronic hepatitis B", "radiation force impulse", "children", and "echo" were frontier topics.

**Conclusions:** Scientometric and visualized analysis of MRE can provide information regarding the knowledge framework, research hotspots, frontier areas, and emerging trends in this field.

**Keywords:** Emerging trends; hotspots; knowledge framework; magnetic resonance elastography (MRE); scientometric analysis

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## Introduction

Viscoelasticity is a mechanical property of soft tissue. Its parameters are related to the structure (1) and physiological state of the tissue, such as muscle tension and compression (2), stiffening of the penis during erection (3), and small changes in brain perfusion due to activity (4). These changes are also related to numerous diseases and responses to treatment (5-10). Therefore, quantitative assessment of tissue viscoelasticity will further our understanding of the physiological condition of an organ, disease diagnosis, monitoring of treatment effects, and prognosis.

Tissue viscoelasticity comprises elasticity and viscosity and can be assessed non-invasively by elastography. Elasticity, representing tissue stiffness, is measured with a shear storage modulus, whereas viscosity, reflecting internal friction between fluid layers under shear stress, is evaluated with a shear loss modulus (11). Elastography is commonly performed using ultrasound (US) or magnetic resonance imaging (MRI) (12). Since Parker *et al.* first used US-based elastography to image the biomechanical properties of tissues over 30 years ago, the use of this technique has expanded rapidly (13). There are 2 major types of elastography: strain elastography and shear wave elastography (SWE). Strain elastography qualitatively measures the tissue deformation caused by compression, but its clinical use is limited due to difficulty assessing tissue deformation in response to an external mechanical force. Meanwhile, SWE quantitatively measures the velocity of propagation of a shear wave through a tissue. Currently available SWE methods include vibration-controlled transient elastography (VCTE), point SWE (pSWE), and 2-dimensional (2D) SWE. The VCTE method measures the unidimensional wave speed of a single mechanical pulse emitted by the probe through the target tissue without images. The A and TM mode maps are used to guide operators to find the ideal location within the tissue. The pSWE method uses acoustic radiation force to displace tissues at a single point within a tissue and measures shear wave speed within small regions of interest, whereas 2D-SWE uses sequential multiple points of displacement to produce a 2D map of stiffness measurement within a larger region of interest (ROI) (14,15). These methods have the advantages of being easily applied by operators, fast to perform, relatively inexpensive, and readily accepted by patients; therefore, they are widely used to evaluate lesions in various organs, such as the liver, breast, prostate, thyroid, spleen, and kidney (16-20). However, these methods are dependent on both the operator and recipient, and the diagnostic performance of US elastography is reduced in obese patients due to insufficient penetration (21).

The accuracy of results obtained via US elastography has been compared to that of magnetic resonance elastography (MRE) (22). In particular, time-harmonic US elastography, which has been used to reach deeper tissues, has been reported to have similar diagnostic accuracy to MRE (23). The MRE technique is a MRI method with a phase-contrast pulse sequence that yields phase difference images, from which the shear modulus based on the wave speed of propagating shear waves is measured and then used to calculate a tissue's viscoelasticity (24,25). The MRE differs from US-based elastography, which assesses Young's modulus (14). Compared with US-based elastography, MRE samples a much larger volume of tissue, is not affected by the mass index, and is not operator dependent (26-28). The most well-established clinical application of MRE is in the detection and quantification of hepatic fibrosis (29), with accurate and reliable results, as well as high intra- and inter-observer agreement (30). Recently, applications for MRE have been extended to the detection of stiffness in the brain, lung, heart, kidney, spleen, and prostate tissues (31-36). Many studies have examined the development of the MRE technique and its clinical application. However, there has been no scientometric analysis and visualization of research in this field.

The CiteSpace software developed by Chen *et al.* (37) is a powerful tool for scientometric and visualization analysis that focuses on exploring key research studies, institutions, and countries, as well as their cooperation. CiteSpace also identifies research hotspots, frontier areas, and research trends in a specified field based on data from the Web of Science database (38). CiteSpace has been widely used in the medical field (39-42).

In the present study, CiteSpace was used to perform a scientometric and visualization analysis of MRE from 1995 to 2021. The aims of this study were to construct an MRE knowledge framework and explore research hotspots, frontier areas, and emerging trends in MRE.

## Methods

### *Data acquisition*

To obtain MRE-related studies published between 1995 and 2021, the Science Citation Index Expanded of the

Web of Science Core Collection (WoSCC) was searched on 22 October 2021 using the following terms: "magnetic resonance elastography" OR "MR elastography" OR "MRE" AND English. Retrieved articles were categorized as either "article" or "review" document types. Subsequently, the abstracts of each of the papers were screened by 2 reviewers (NC and YZ) jointly to identify studies on human participants. Studies performed on animals and those not related to MRE were excluded. Finally, the raw data for the identified papers were downloaded as full-text documents with references and in plain-text format, including the title, abstract, keywords, authors' names, institutions, countries, year of publication, and references.

This study was designed as a literature review; neither ethics approval nor informed consent was applicable.

### *Analytical methods*

Microsoft (Bellevue, WA, USA) Excel 2016 and CiteSpace V version 5.8.R3 (downloaded from http://cluster.cis.drexel.edu/~cchen/citespace/) were used to analyze the downloaded data. Excel 2016 was used to draw annual maps of published literature on MRE from 1995 to 2021, revealing trends in the number of articles published by year. CiteSpace V was used to analyze the author, institution, and country cooperative networks, to perform reference co-citation analysis to display the MRE knowledge framework, and to conduct keyword co-occurrence and burst keyword analyses to explore research trends, hotspots, and research frontiers in the field. The CiteSpace parameters were set as follows: the publication date of the articles (time slicing) ranging from January 1995 to October 2021, "years per slice" = 1; the term "source" included the title, abstract, author keywords, and keywords plus; Strength = "Cosine", Scope = "Within slices", and Top N=30; "Minimum Spanning Tree" and "Pruning Sliced networks" for the cooperation network, and "pathfinder" and "pruning the merged network" for the reference co-citation and keywords co-occurrence analyses; Visualization was set as "Cluster View Static" and "Show Merged Network".

Networks are characterized by the central parameters of CiteSpace, including node, betweenness centrality, and burst detection. Nodes in the cooperation network maps represent authors, institutions, or countries, whereas in keyword networks they represent keywords. The size of a node is proportional to the number of articles published or the frequency of keyword occurrence, and the color of nodes indicates the years of occurrence or citation. Betweenness centrality, a quantitative indicator of the influence of a node in the network, is defined as the fraction of shortest paths between node pairs that pass through a given node of interest (43). The higher the betweenness centrality of the node, the greater its importance in the network, and these nodes appear with a purple rim in the output maps. The burst detection algorithm can be adapted to detect sharp increases in interest in a specialty (44). The degree of burst is represented by burst strength, and keywords with a higher strength are often identified as hotspots or turning points in the field.

Keywords are words or phrases that reflect the characteristics of a paper. A reference refers to the literature cited when writing papers or specific research works. It is the basis of research progress in a certain field. Therefore, the knowledge framework is derived from the reference co-citation network, keyword clusters of cited references, and the highly cited reference literature (45). Co-occurrence keywords analysis is commonly used to explore research hotspots and emerging trends, whereas keyword burst detection is used to discover frontier areas (46,47). In the present study, hotspots are represented by keywords with higher frequency and betweenness centrality, whereas emerging trends are represented by the evolution of keywords. Frontier areas are represented by keyword bursts with a higher strength.

## Results

### *Article selection and publication year*

In all, 2,825 studies were identified from the WoSCC search, with 2,353 studies included after refinement using the "article" and "review" keywords and the exclusion of meeting abstracts, early access papers, proceedings papers, editorial material, corrections, notes, letters, and data papers. After reading each abstract, a further 1,117 studies were excluded, of which 8 were associated with animal experiments and 1,109 were not related to MRE. Thus, 1,236 studies were subjected to CiteSpace analysis in the present study (*Figure 1*).

Three distinct time periods were demonstrated for publications on MRE (*Figure 2*). The first period was between 1995 and 1999, when 1 article on MRE was published per year. During the second period, from 2000 to 2010, the number of articles published increased steadily and slowly, and was maintained at 6–36 papers annually. During the third period [2011–2021], the number of articles published grew at a remarkable rate, increasing from 34 in 2011 to 140 in 2020. At the time of writing, 138 articles had been published in 2021.

### *Collaboration network analysis*

#### Analysis of author cooperation

The network map of coauthorship (*Figure 3*) shows that 1,236 articles were written by 726 authors; 675 authors published <10 articles, 32 published 10–20 articles, 12 published 21–50 articles, and 7 published >50 articles. The top 10 authors were Richard Ehman (n=185 articles), Ingolf Sack (n=130), Juergen Braun (n=109), Ralph Sinkus (n=82), Kevin Glaser (n=78), Armando Manduca (n=71), Meng Yin (n=54), Sudhakar Venkatesh (n=49), Jing Guo (n=38), and Rohit Loomba (n=37), accounting for 67.4% of all articles included in this analysis. Neil Roberts, John Huston III, Kevin Glaser, Dieter Klatt, Philippe Garteiser, and Jens Wuerfel played a positive role in authors' cooperation because of their higher centrality (*Table 1*). Richard Ehman, Kevin Glaser, Meng Yin, Armando Manduca, Sudhakar Venkatesh, Rohit Loomba, John Huston III, and Dieter Klatt were from the US; Ingolf Sack, Juergen Braun, Jing Guo, and Jens Wuerfel were from Germany; Ralph Sinkus and Neil Roberts were from the UK; and Philippe Garteiser was from France.

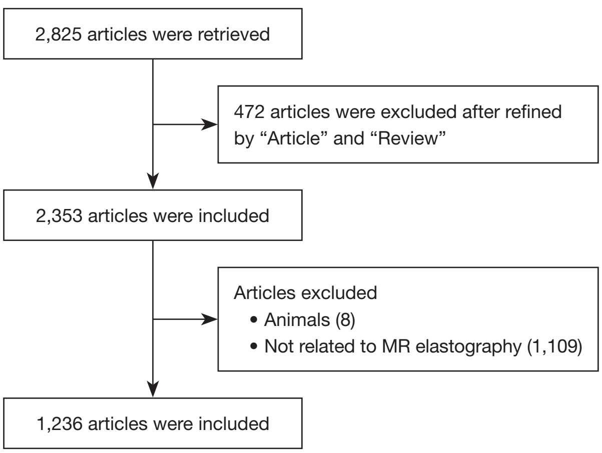


**Figure 1** Flow chart showing data acquisition.

#### Analysis of institutional cooperation

A total of 540 institutions had contributed to MRE research (*Figure 4*). The top 10 institutions published 679 articles (*Table 2*), accounting for 54.9% of all articles included in this study. The Mayo Clinic published 240 papers, and was ranked the publishing institution, followed by Charité, University of Illinois, Dartmouth College, and University of California San Diego. Each of these institutions published ≥50 papers. King's College London, University of Delaware, Dartmouth Hitchcock Medical Center, Cincinnati Children's Hospital Medical Center, and University of Ohio State each published 26–33 papers. In terms of centrality, Mayo Clinic (0.61), Charité (0.20), King's College London (0.15), and University of California San Diego (0.14) played an important role in institutional cooperation.

Eight of the top 10 institutions are in the US (Mayo Clinic, University of Illinois, Dartmouth College, University of California San Diego, University of Delaware, Dartmouth Hitchcock Medical Center, Cincinnati Children's Hospital Medical Center, and University of Ohio State); Charité is in Germany; and King's College London is in the UK.

#### Analysis of country cooperation

The network map of country cooperation showed that 40

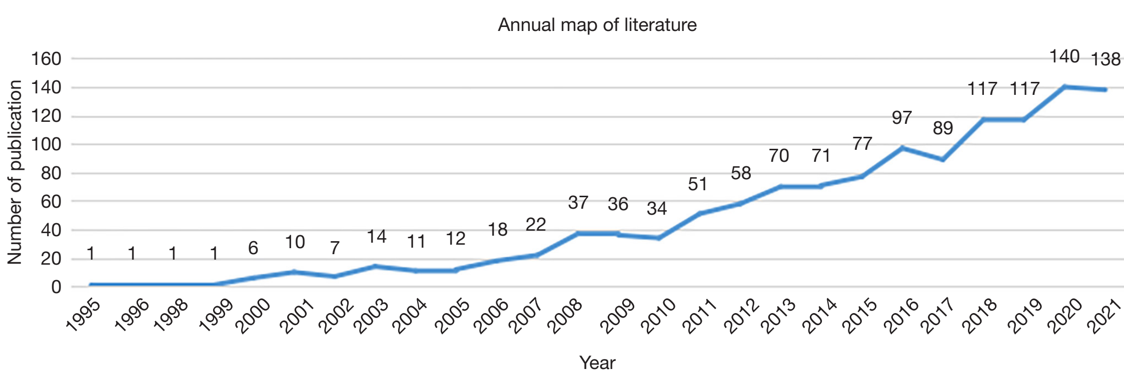


**Figure 2** Number of studies on MRE published annually from 1995 to 2021. MRE, magnetic resonance elastography.

 

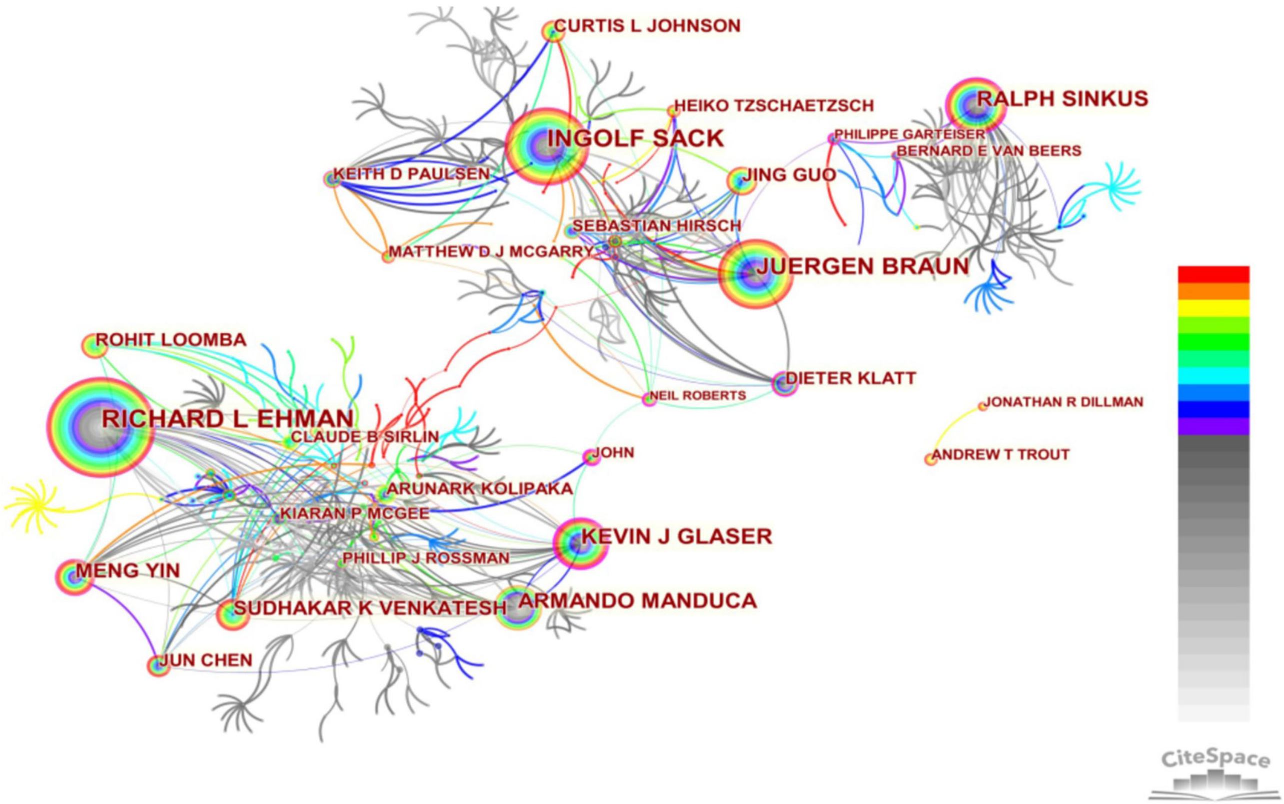


**Figure 3** Map of author cooperation networks in magnetic resonance elastography from 1995 to 2021. Each node represents an author, and the node size is proportional to the number of the articles published. The colored rings in each node indicate years of publication, ranging from cool (early) to warm (recent); purple trims appear in those nodes with higher betweenness centrality. Each link represents the connection between nodes, with the thickness of the links indicating the strength of the cooperative relationship.

**Table 1** Top 10 published authors on MRE studies, and top 10 authors with higher centrality from 1995 to 2021

| Ranking | Author | No. of papers | Country | Author | Centrality | Country |
|---|---|---|---|---|---|---|
| 1 | Richard Ehman | 185 | USA | Neil Roberts | 0.53 | UK |
| 2 | Ingolf Sack | 130 | Germany | John Huston III | 0.51 | US |
| 3 | Juergen Braun | 109 | Germany | Kevin J. Glaser | 0.50 | US |
| 4 | Ralph Sinkus | 82 | UK | Philippe Garteiser | 0.32 | France |
| 5 | Kevin Glaser | 78 | USA | Jens Wuerfel | 0.32 | Germany |
| 6 | Armando Manduca | 71 | USA | Dieter Klatt | 0.31 | USA |
| 7 | Meng Yin | 54 | USA | Ralph Sinkus | 0.28 | UK |
| 8 | Sudhakar Venkatesh | 49 | USA | Peter Martus | 0.26 | Germany |
| 9 | Jing Guo | 38 | Germany | Ingolf Sack | 0.19 | Germany |
| 10 | Rohit Loomba | 37 | USA | Keith Paulsen | 0.19 | USA |

MRE, magnetic resonance elastography.

 

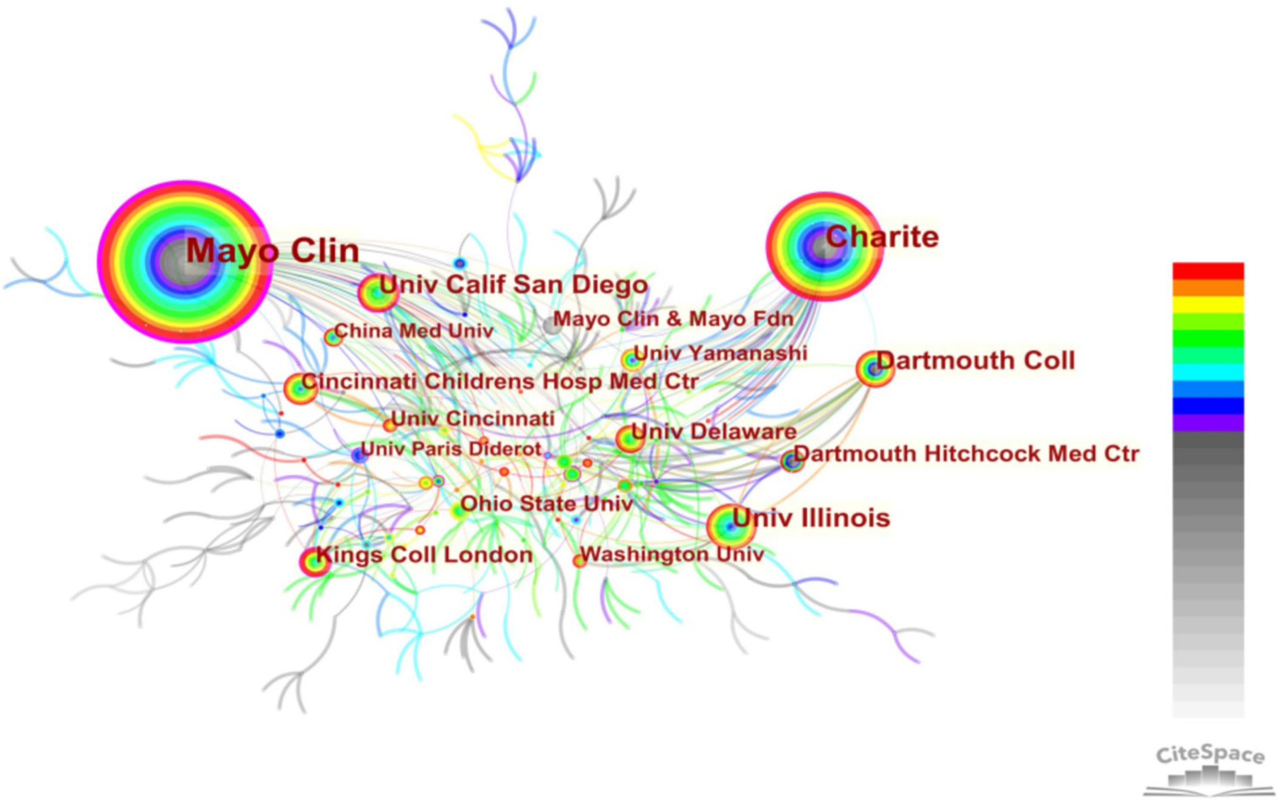


**Figure 4** Map of institution cooperation networks, with 540 nodes and 653 links, in MRE from 1995 to 2021. Each node represents an institution, with the size of the node proportional to the number of articles published. The colored rings in each node indicate years of publication, ranging from cool (early) to warm (recent); purple trims appear in nodes with higher betweenness centrality. Each link represents the connection between nodes, with the thickness of the links indicating the strength of the cooperative relationship. MRE, magnetic resonance elastography.

**Table 2** Top 10 countries and institutions for MRE studies from 1995 to 2021

| Ranking | Country | No. of papers | Centrality | Institution | No. of papers | Centrality |
|---|---|---|---|---|---|---|
| 1 | USA | 631 | 0.61 | Mayo Clinic | 240 | 0.61 |
| 2 | Germany | 202 | 0.24 | Charité | 131 | 0.20 |
| 3 | France | 134 | 0.40 | University of Illinois | 56 | 0.04 |
| 4 | China | 105 | 0.07 | Dartmouth College | 52 | 0.04 |
| 5 | UK | 96 | 0.06 | University of California San Diego | 50 | 0.13 |
| 6 | Japan | 91 | 0.20 | King's College London | 33 | 0.15 |
| 7 | Canada | 73 | 0.13 | University of Delaware | 32 | 0.04 |
| 8 | South Korea | 57 | 0.00 | Dartmouth Hitchcock Medical Center | 31 | 0.01 |
| 9 | Australia | 30 | 0.06 | Cincinnati Children's Hospital Medical Center | 28 | 0.02 |
| 10 | Switzerland | 29 | 0.12 | University of Ohio State | 26 | 0.03 |

MRE, magnetic resonance elastography.

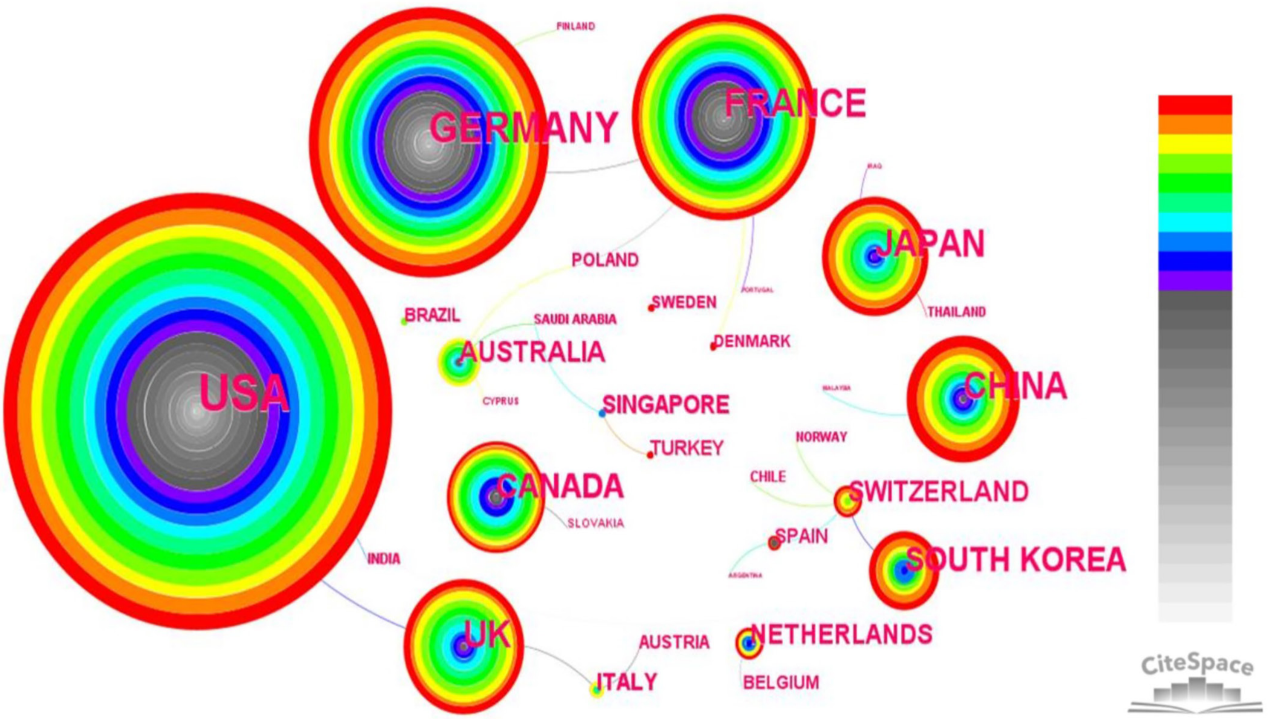


**Figure 5** Map of country cooperation networks, with 40 nodes and 104 links, in MRE from 1995 to 2021. Each node represents a country, with the size of the node proportional to the number of articles published. The colored rings in each node indicate years of publication, ranging from cool (early) to warm (recent); purple trims appear in those nodes with higher betweenness centrality. Each link represents the connection between nodes, with the thickness of the links indicating the strength of the cooperative relationship. MRE, magnetic resonance elastography.

countries had participated in MRE research (*Figure 5*). As indicated in *Table 2*, the USA had contributed the highest number of articles (n=631), followed by Germany (n=202), France (n=134), China (n=105), UK (n=96), Japan (n=91), Canada (n=73), South Korea (n=57), Australia (n=30), and Switzerland (n=29). Of these countries, the USA, France, Germany, and Japan played important roles in this field, with centrality values of 0.61, 0.40, 0.24, and 0.20, respectively.

### *Analysis of co-citation references*

The 24,347 distinct references formed a network map of co-citation references with 639 nodes, 2,100 links, and 48 clusters obtained via reasonable clustering using specific keywords (*Figure 6*). In the top 10 clusters (*Table 3*), "liver fibrosis" ranked first, with 86 members, followed by "springpot" (n=84), "brain" (n=62), "radiofrequency" (n=55), "myofascial pain" (n=46), "MR imaging" (n=42), "elasticity reconstruction" (n=40), "mechanical" (n=29), "elastic modulus" (n=25), and "contraction" (n=24).

The top 15 references with higher citations are presented in *Table 4*. The article published by Venkatesh *et al.* (48) was cited 94 times, whereas the other 14 articles (27,29,49-60) were cited between 52 and 85 times. Some 7 articles were from the cluster "liver fibrosis", 7 were from the "springpot" cluster, and 1 was from the "brain" cluster.

### *Analysis of keyword co-occurrence*

The map of keyword co-occurrence, with 294 nodes and 1,259 links, was established from the qualified 1,195 records (*Figure 7A*). "Magnetic resonance elastography" had the highest frequency of use (n=843 times), followed by "hepatic fibrosis" (n=366), "stiffness" (n=239), "non-invasive assessment" (n=187), and "tissue" (n=167). Nodes representing important keywords were marked with a purple circle; "in vivo" and "skeletal muscle" were identified

 

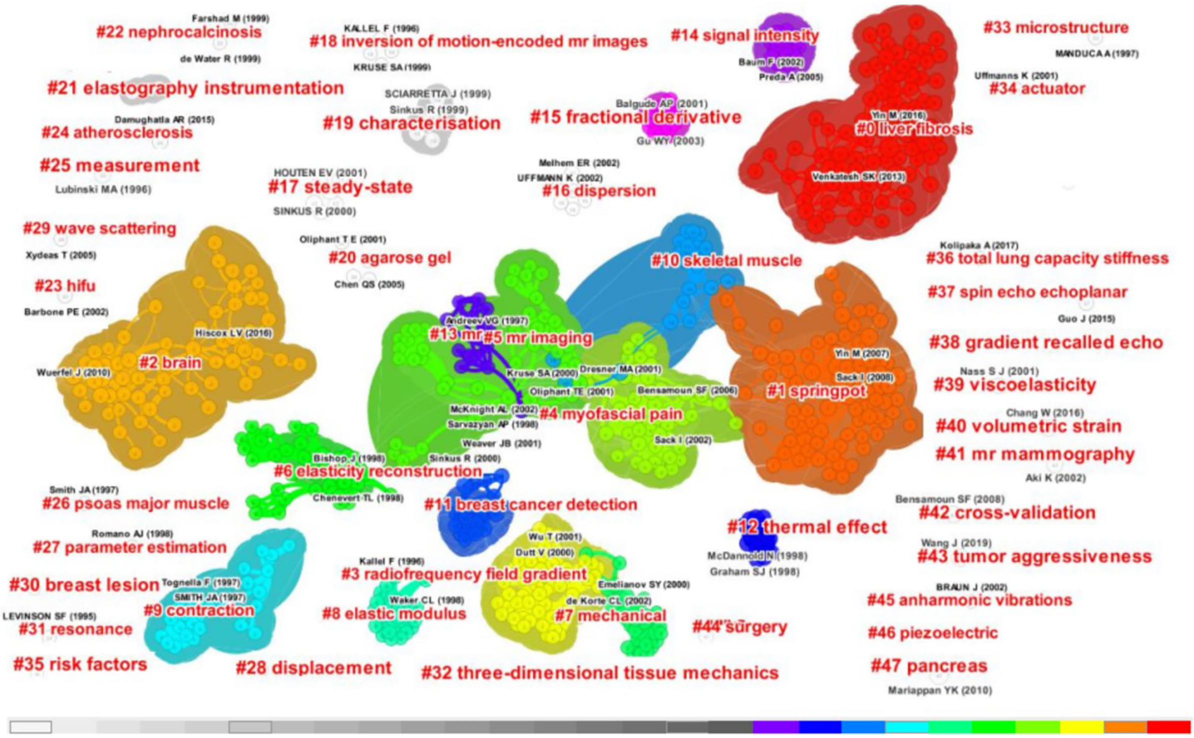


**Figure 6** Cluster visualization of the reference co-citation network, with modularity Q=0.84 and mean silhouette S=0.91 (indicating that the classification was reasonable and the interior of the cluster was uniform), in MRE from 1995 to 2021. The different-colored shapes represent different clusters, with the colors indicating the years they appeared. The clusters represent the frequency of the keywords in the publications. The smaller the sequence number of the cluster, the higher the frequency. The papers [name (year)] appeared in each cluster were the result of the parameter related to co-citation frequency set by an operator. MRE, magnetic resonance elastography.

**Table 3** Top 10 clusters of reference co-citation networks in MRE from 1995 to 2021

| Cluster ID | Size | Silhouette value | Mean year | Cluster label | Label (LLR) |
|---|---|---|---|---|---|
| 0 | 86 | 0.94 | 2014 | Liver fibrosis | Liver fibrosis; brain; transient elastography; non-alcoholic fatty liver disease |
| 1 | 84 | 0.90 | 2006 | Springpot | Springpot; acoustic radiation force; brain viscoelasticity; dynamic contrast-enhanced MR imaging; normal pressure hydrocephalus |
| 2 | 62 | 0.95 | 2013 | Brain | Brain; hippocampus; viscoelasticity; liver fibrosis; aging |
| 3 | 55 | 0.95 | 2000 | Radiofrequency | Radiofrequency field gradient; vibrations; compression test; anharmonic vibrations; non-linear harmonics |
| 4 | 46 | 0.98 | 2001 | Myofascial pain | Myofascial pain; elastic properties; finite element modeling; skeletal muscle; shear stiffness |
| 5 | 42 | 0.93 | 2001 | MR imaging | MR imaging; prostate gland; inversion algorithms; plantar mechanical properties; breast cancer detection |
| 6 | 40 | 0.97 | 1995 | Elasticity reconstruction | Elasticity reconstruction; subzone technique; model-based imaging; regularized inversion techniques; finite element method |
| 7 | 29 | 0.92 | 1999 | Mechanical | Mechanical; arteriosclerosis; stress; ultrasonography; magnetic resonance elastography |
| 8 | 25 | 0.97 | 1997 | Elastic modulus | Elastic modulus; MR-elastography; tumor detection; tissue characterization; magnetic resonance elastography |
| 9 | 24 | 1 | 1997 | Contraction | Contraction; muscle; mechanical properties; Magnetic resonance imaging; elastography |

MRE, magnetic resonance elastography; LLR, log-likelihood ratio; MR, magnetic resonance.

 

**Table 4** Top 15 references (27,29,48-60) with the highest number of citations in MRE from 1995 to 2021

| Ranking | No. of citations | Centrality | Year | Reference |
|---|---|---|---|---|
| 1 | 94 | 0.01 | 2013 | Venkatesh *et al.* (48) |
| 2 | 85 | 0.02 | 2016 | Yin *et al.* (27) |
| 3 | 81 | 0.11 | 2007 | Yin *et al.* (51) |
| 4 | 81 | 0.05 | 2015 | Singh *et al.* (55) |
| 5 | 70 | 0.01 | 2008 | Sack *et al.* (59) |
| 6 | 69 | 0.02 | 2016 | Imajo *et al.* (54) |
| 7 | 65 | 0.01 | 2006 | Rouvière *et al.* (49) |
| 8 | 65 | 0.04 | 2014 | Loomba *et al.* (29) |
| 9 | 62 | 0.07 | 2011 | Chen *et al.* (53) |
| 10 | 62 | 0.02 | 2008 | Huwart *et al.* (50) |
| 11 | 60 | 0.04 | 2010 | Wuerfel *et al.* (58) |
| 12 | 59 | 0.05 | 2010 | Asbach *et al.* (52) |
| 13 | 55 | 0.14 | 2008 | Green *et al.* (56) |
| 14 | 54 | 0.08 | 2008 | Kruse *et al.* (57) |
| 15 | 52 | 0.19 | 2009 | Sack *et al.* (60) |

MRE, magnetic resonance elastography.

as the first keywords with the highest centrality (0.23), followed by "magnetic resonance elastography" (0.17), "acoustic strain wave" (0.13), and "stiffness" (0.12; *Table 5*).

There were 16 clusters in the keyword co-occurrence clustering map (*Figure 7B*), which were summarized into 2 categories: (I) MRE technique ("acoustic strain wave", "MRI", "MRE" and "viscoelastic tissue characterization"); and (II) MRE clinical application ("brain", "hepatic fibrosis", "liver tumors", "behavior", "in vivo", "neuromuscular compartment", "liver imaging", "MAS", "pediatric hydrocephalus", "hyperthyroidism", "HIV", and "head"; *Table 6*).

The time zone view of the co-occurrence of keywords (*Figure 8*) shows the top 10 high-frequency keywords and the top 10 high-centrality keywords between 1995 and 2011. The earliest research direction was "tissue" in 1995, followed by "magnetic resonance elastography" and "acoustic strain wave" in 1998; "disease", "elasticity", and "reconstruction" in 2000; "in vivo", "MRI", "model", "skeletal muscle", and "visualization" in 2001; "stiffness" in 2002; "breast lesion", "breast cancer", and "cancer" in 2003; "viscoelasticity" and "behavior" in 2004; "hepatic fibrosis", "non-invasive assessment", and "biopsy" in 2006; "diagnosis" and "portal hypertension" in 2007; "inversion", "brain", and "quantification" in 2008; "hepatic steatosis" in 2009; "diagnostic performance", "mechanical property", and "hepatocellular carcinoma" in 2010; and "repeatability" in 2013. Since 2014, other keywords have appeared, such as "diagnostic accuracy" and "chronic hepatitis B"; however, these keywords have lower frequency and centrality.

### *Analysis of the keyword burst*

*Figure 9* shows the top 25 keywords with the strongest citation bursts. The first keyword burst was "tissue", which started in 1995 and ended in 2008. The second keyword burst was "acoustic strain wave", with the highest burst strength (19.71), which appeared in 1998 and lasted until 2008. From 2000 to 2017, 15 keywords bursts disappeared consecutively. In the past 4 years, 8 keyword bursts have received significant attention: "diagnostic performance", "diagnostic accuracy", "hepatic steatosis", "chronic hepatitis B", "radiation force impulse", "children", "elastography", and "echo".

## Discussion

### *General information*

Since Muthupillai *et al.* (61) introduced MRE in 1995, this method has become a useful tool for studying a tissue's physiological or pathological state. Technological improvements to the technique and its extended application in various organs have led to marked increases in the number of MRE-related articles published each year. This trend is consistent with the history of MRE (Appendix 1).

In this study, we identified articles published by 726 authors from 540 institutions in 40 countries. The USA, Germany, and France have made important contributions to research related to MRE and are central collaborators with other countries. Some 8 of the top 10 institutions and 8 of top 15 important authors (with higher number of papers or higher centrality) were from the USA; 1 institution and 4 authors were from Germany, and 1 author was from France.

### *Knowledge framework*

The 639 keywords extracted from 24,347 cited references were grouped into 48 clusters, which, along with 15 highly frequently cited references, formed the knowledge

 

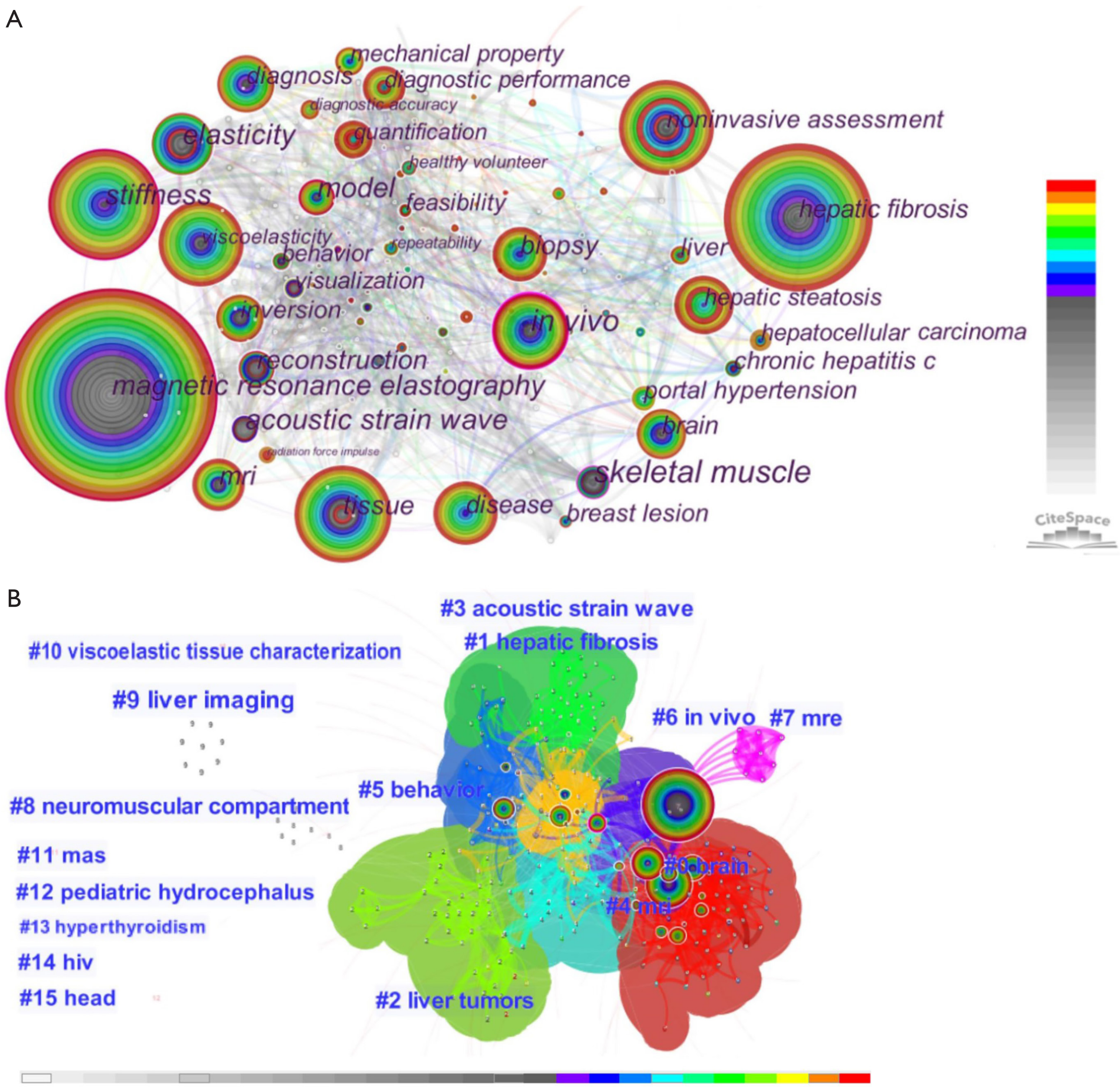


**Figure 7** Co-occurrence keyword networks in MRE from 1995 to 2021. (A) Map of co-occurring keywords. Each node represents a co-occurring keyword, with the size of the node proportional to the number of articles published. The colored rings in each node indicate years of publication, ranging from cool (early) to warm (recent); purple trims appear in those nodes with higher betweenness centrality. (B) Cluster analysis map of co-occurring keywords, with overall modularity Q=0.54 and mean silhouette S=0.78 (indicating that the classification was reasonable and the interior of the cluster was uniform). The network was divided into 16 clusters. The different-colored shapes represent different clusters, with the colors indicating years of publication. The cluster number represents the frequency of the keywords in the publications. The smaller the cluster number, the higher the frequency. MRE, magnetic resonance elastography.

**Table 5** Top 10 high-frequency keywords and top 10 high centrality keywords in MRE from 1995 to 2021

| Ranking | Keyword | Frequency | Ranking | Keyword | Centrality |
|---|---|---|---|---|---|
| 1 | Magnetic resonance elastography | 843 | 1 | In vivo | 0.23 |
| 2 | Hepatic fibrosis | 366 | 2 | Skeletal muscle | 0.23 |
| 3 | Stiffness | 239 | 3 | Magnetic resonance elastography | 0.17 |
| 4 | Non-invasive assessment | 187 | 4 | Acoustic strain wave | 0.13 |
| 5 | Tissue | 167 | 5 | Stiffness | 0.12 |
| 6 | Viscoelasticity | 145 | 6 | Model | 0.11 |
| 7 | In vivo | 143 | 7 | Elasticity | 0.10 |
| 8 | Disease | 138 | 8 | Reconstruction | 0.10 |
| 9 | Hepatic steatosis | 122 | 9 | Disease | 0.09 |
| 10 | Elasticity | 112 | 10 | MRI | 0.09 |

MRE, magnetic resonance elastography; MRI, magnetic resonance imaging.

**Table 6** Top10 clusters of keywords in MRE from 1995 to 2021

| Cluster ID | Size | Silhouette value | Mean year | Cluster label | Label (LLR) |
|---|---|---|---|---|---|
| 0 | 62 | 0.81 | 2010 | Brain | Brain; liver fibrosis; transient elastography; biopsy; disease |
| 1 | 44 | 0.67 | 2003 | Hepatic fibrosis | Hepatic fibrosis; reconstruction; finite element modeling; liver fibrosis; strain imaging |
| 2 | 38 | 0.78 | 2008 | Liver tumor | Liver tumors; diffusion MRI; contrast agent; Diffusion-weighted imaging; prostate imaging |
| 3 | 36 | 0.81 | 2005 | Acoustic strain wave | Acoustic strain wave; radiofrequency field gradient; thigh muscle; actuator; contraction |
| 4 | 32 | 0.72 | 2008 | MRI | MRI; strain; myocardium; accurate; magnetic resonance elastography |
| 5 | 25 | 0.71 | 2009 | Behavior | Brain; behavior; MRI; viscoelasticity; disease |
| 6 | 21 | 0.89 | 2007 | In vivo | In vivo; viscoelastic parameters; transient elastography; feasibility; temperature |
| 7 | 10 | 0.95 | 2001 | MRE | MRE; meningioma; MR elastography; magnetic resonance elastography; complication |
| 8 | 9 | 0.96 | 2006 | Neuromuscular compartment | Neuromuscular compartment; human skeletal muscle; cross sectional area; spinal cord injury; relaxation time |
| 9 | 8 | 1 | 2010 | Liver image | Liver imaging; dynamic contrast enhanced MR imaging; MR spectroscopy; functional MR imaging; apparent diffusion coefficient |

LLR, log-likelihood ratio; MR, magnetic resonance; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging.

framework for the MRE field. In the top 10 clusters, Cluster numbers 0, 2, and 3 indicated that MRE was mainly used in the case of liver fibrosis, brain, and myofascial pain, respectively; the other clusters were focused on MRE techniques.

MRE is a non-invasive MRI technique that reflects the complex interactions between cells and the extracellular matrix (62). An MRE consists of 3 components: a mechanical wave generator, a phase-contrast magnetic resonance (MR) sequence for acquiring wave propagation, and an inversion algorithm to process the effects of the shear waves on mechanical parameters.

The sources of the mechanical waves can be either external or internal. Most MRE methods use external sources of mechanical waves, such as electromagnetic coils, piezoelectric stacks, or pneumatic actuators (61,63-65).

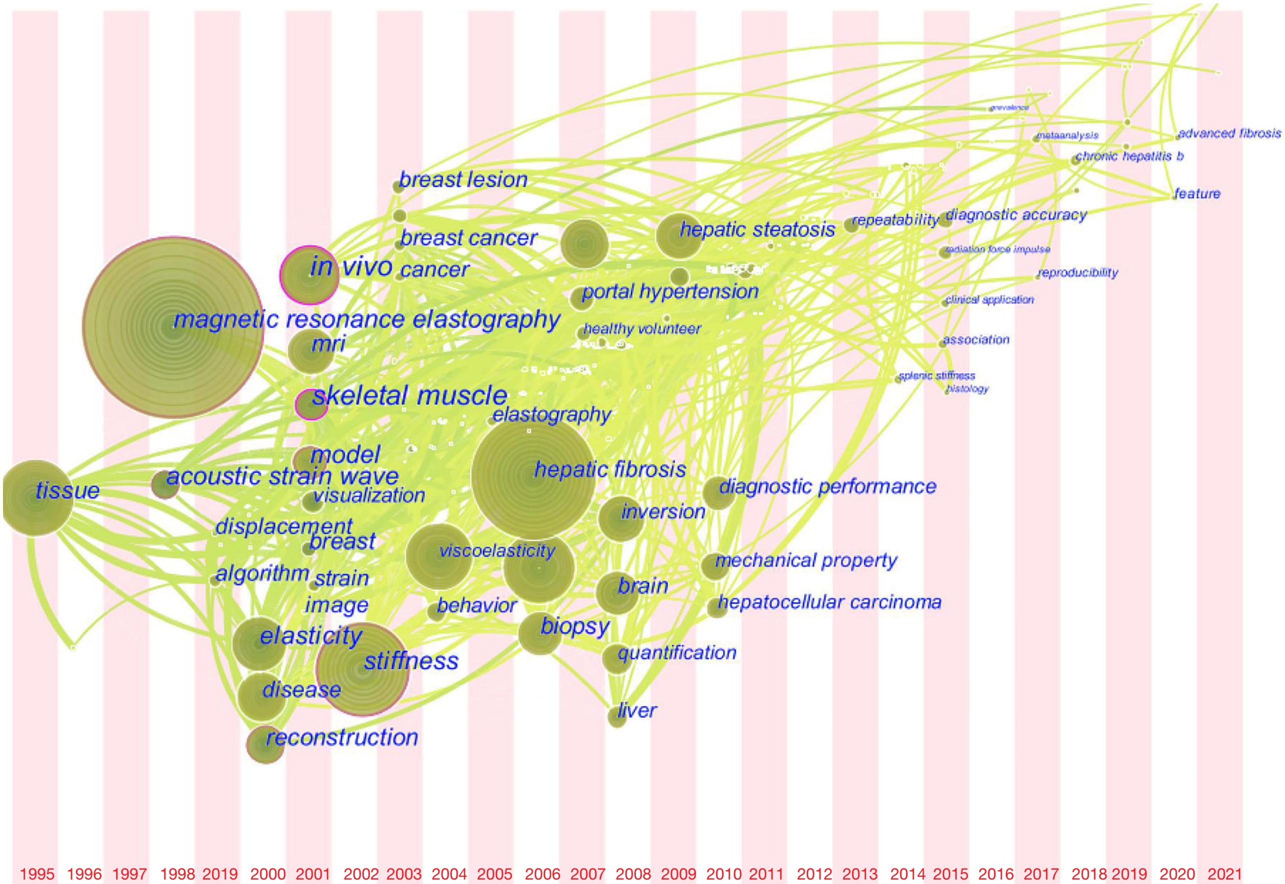


**Figure 8** Time zone of co-occurring keywords in MRE from 1995 to 2021. MRE, magnetic resonance elastography.

Both electromagnetic coils and piezoelectric stacks generate high-frequency vibrations and have been primarily used in animal research. The pneumatic actuator system consists of a loudspeaker placed outside the MR scanner room and a passive driver on the surface of the target tissue. This system is commonly used in clinical applications. Internal mechanical waves primarily originate from physiological motion, such as a beating heart (66).

Both longitudinal and shear waves exist simultaneously when a mechanical wave is applied to the tissue surface. Because the velocity of longitudinal wave propagation is very high compared with that of shear wave propagation, it does not vary significantly in different soft tissues. The MRE commonly measures the velocity of shear wave propagation to explore the mechanical properties of the tissues (22); therefore, longitudinal waves, which are confounding factors, must be removed by a spatial high-pass filter or the curl of the data (67). The MR pulse sequences including gradient-recalled echo or spin echo with/without echo-planar imaging (EPI), balanced steady-state free precession (SSFP), and spiral sequence (68-71) can capture the propagation velocities of shear waves, which are then transformed into biological properties via linear or non-linear inversion algorithms.

Monofrequency MRE uses a 20–100 Hz monofrequency wave (72) through target tissue. It assumes that the measured tissue is nearly incompressible and isotropic, and thereby shear wave velocity is the only parameter used to determine the stiffness of tissue linearly, without a specific rheological model to calculate storage and loss modulus. For traditional monofrequency MRE, the frequency of the motion-encoding gradient (MEG) is synchronized with monofrequency mechanical excitation, and the minimum echo time depends on the duration of the MEG. When low-vibration frequencies are used, the minimum echo time is increased and the images acquired can be prone to a low phase-to-noise ratio, especially in tissues with short $T_2$ relaxation, such as the liver with

 

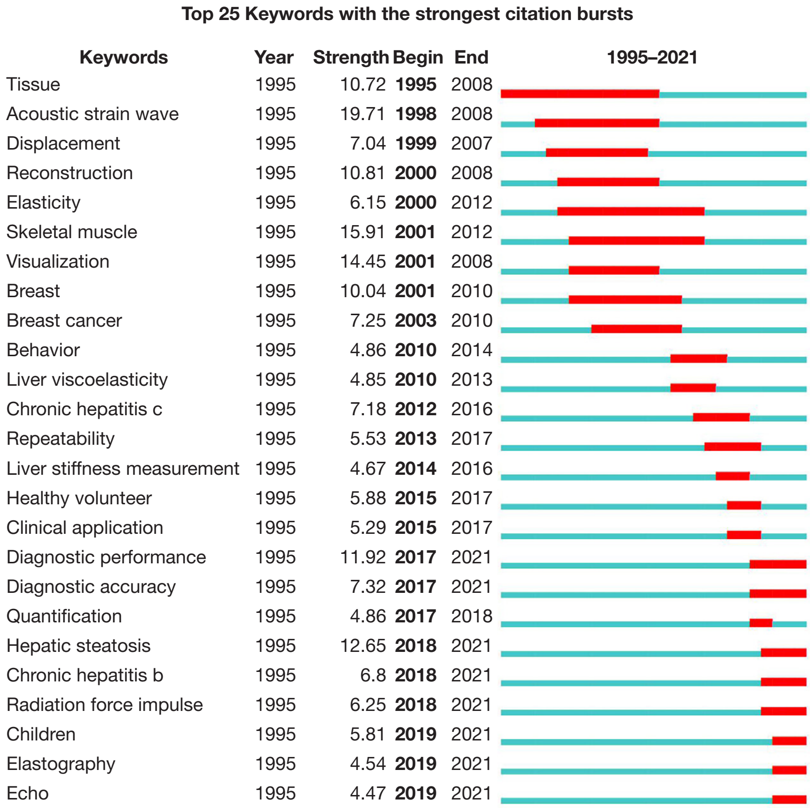


**Figure 9** The top 25 keywords with the strongest citation burst in MRE from 1995 to 2021. The green lines indicate the time from 1995 to 2021, with the red lines representing the time span of the keyword burst. MRE, magnetic resonance elastography.

iron overload. However, using novel EPI-based sequences to image quickly, the feasibility and clinical potential of cardiac monofrequency MRE (73) and functional (f)MRE (74) have been demonstrated. To evaluate tissue elasticity accurately, shear wave velocities in all 3 spatial directions are measured to acquire a complete data set. Since nearly all tissues/organs have different wave speeds at different frequencies, multifrequency MRE is often preferred to quantify the viscoelastic properties of these tissues/organs. Three models, namely Voigt, Maxwell, and springpot, are commonly used to analyze the data; the springpot model in particular better represents soft tissue behavior in the frequency range of MRE (75). However, in clinical practice, with limited scan time, monofrequency MRE has also been shown to be useful in characterizing tissue viscoelasticity (76).

With regard to MRE, the following should be noted:

- ❖ Achieving good-quality MRE requires the frequency and amplitude of the mechanical excitation to be in an appropriate range (22) and the wavelength/pixel ratio to be at 6–9 voxels per wavelength (77).
- ❖ In MRE, the density of the soft tissue is assumed to be equal to that of water (1.0 g/cm$^3$); however, this assumption does not hold for lung MRE, where the tissue density is too low, and an exact density value is required (22).
- ❖ Following a meal, water intake, or activity, the biomechanical properties of the liver, spleen, kidney, and brain can change (78-80); therefore, patients should undergo MRE examinations during rest and in a fasting state.

The top 15 articles had the highest citation frequency. Venkatesh *et al.* (48) reviewed the technique, clinical application, and potential future application of liver MRE. Rouvière *et al.* (49) investigated the feasibility of MRE in volunteers and patients with chronic liver diseases. The success rate of liver MRE was estimated to be 94.4% (27,50). Others have studied values of conventional or multifrequency MRE to assess hepatic fibrosis (51,52), finding that the diagnostic performance of conventional or multifrequency MRE in determining the stage of liver fibrosis increased with the stage of fibrosis. Chen *et al.* (53) used MRE for the early detection of non-alcoholic steatohepatitis and reported that the mean hepatic stiffness for patients with inflammatory non-alcoholic fatty liver disease (NAFLD) was greater than that of patients with simple steatosis and lower than that of patients with fibrosis. Two studies (29,54) and a meta-analysis (55) have provided further evidence that MRE can be used to accurately diagnose advanced fibrosis in NAFLD patients.

In 2007, Green *et al.* (56) used MRE to measure the complex shear modulus in brain tissue *in vivo* and confirmed the validity of this technique. Concomitantly, Kruse *et al.* (57) obtained normative human cerebral data from different age groups using the shear modulus of MRE, with no age dependence found. However, the most acknowledged trend is brain softening with aging (81). Wuerfel *et al.* (58) demonstrated that brain parenchymal viscoelasticity was significantly reduced in patients with mild multiple sclerosis (MS) compared with healthy volunteers. In terms of a rheological model, Sack *et al.* (59) observed that MRE with Voigt's model was inadequate for assessing the behavior of viscoelastic brain tissue, and that multifrequency MRE with the springpot model provided sensitive measurements (60).

### *Research hotspots, frontiers, and emerging trends*

#### Research hotspots

Based on the results of CiteSpace, the 2 main research hotspots in the field of MRE were summarized as "MRE technique" and "clinical application".

***MRE technique***

MRE is a non-invasive MRI method to quantitatively assess a tissue's viscoelasticity or stiffness. Three technical components work together to complete this task: propagation of mechanical shear waves through the tissues of interest, MRE imaging sequences, and inversion algorithms. Shear waves produced by an actuator and their frequency have important implications for the contrast and resolution of stiffness maps. Optimal frequency will differentiate small lesions from surrounding tissues and improve sensitivity (82). Many MRE imaging sequences and emerging MRI technologies (68-71,83-91) have been used to shorten acquisition times, increase the coverage volume of the ROI, and obtain good resolution images, especially MRI scanners with newer techniques. Post-processing of acquired images to create quantitative stiffness maps requires specialized inversion algorithms. However, there are no standardized methods reported in the literature that are used across vendors and groups. They are also optimized over time (Appendix 1). These components continue to evolve, leading to decreased scan times and improved spatial resolution that, in turn, increase the sensitivity and accuracy of diagnosis, such that MRE can be widely used in clinical practice.

Apart from "magnetic resonance elastography", the main research hotspots associated with MRE techniques from 1995 to 2021 were "stiffness", "non-invasive assessment", "tissue", "in vivo", "acoustic strain wave", "viscoelasticity", "elasticity", "model", "reconstruction", and "mri".

***Clinical application***

MRE research hotspots in the liver are "hepatic fibrosis" and "hepatic steatosis", categorized as Cluster 0. Liver elastography is the first clinical application of MRE for the detection and staging of liver fibrosis. A standardized MRE protocol and agreement for the staging of fibrosis worldwide has been established (92). Liver elastography is currently the most accurate non-invasive imaging method for the initial detection and quantitative staging of fibrosis (92). It can differentiate significant fibrosis (stage ≥2) from mild fibrosis (stage 0–1) with >92% accuracy and a positive predictive value of >93%, and diagnose cirrhosis (stage 4) with >95% accuracy and a negative predictive value of >98% (52). MRE can also be used to evaluate NAFLD, specifically to differentiate NAFLD from steatohepatitis. A streamlined protocol has been established to calculate a virtual NAFLD activity score to estimate steatosis, inflammation/ballooning, and fibrosis (93).

Research hotspots in the brain are found in Cluster 1 (springpot) and Cluster 2 (brain). Neurological disorders are one of the most important public health concerns worldwide. MRE, as a non-invasive measurement of brain mechanical properties, has been used to investigate various neurological disorders, including intracranial tumors, and diffuse diseases such as dementia and MS. Wuerfel *et al.* (58) first studied brain stiffness in patients with MS and showed that global stiffness was decreased in MS patients compared with control subjects. Similarly, decreased brain stiffness has been seen in most neurodegenerative diseases, such as Alzheimer's disease (94). For intracranial tumors, MRE not only accurately predicts tumor stiffness and helps surgeons with preoperative planning, but also measures heterogeneity within the tumor (95). Except for meningioma, which exhibits increased stiffness, brain tumors are reported as a softening of the mechanical rigidity of tissue (96). Furthermore, MRE can measure tumor adherence to surrounding tissues (97,98). More recently, 3-dimensional MRE has enabled evaluation of specific neuroanatomical regions, such as the corpus callosum, hippocampus, and corticospinal tract (99-101). However, there is still much work needed in this area, especially in establishing a brain MRE protocol for clinical application.

The research hotspot in "skeletal muscle" is categorized as Cluster 4. The US-based elastography has been widely used to investigate changes in muscle stiffness because it non-invasively provides information on muscle functional status, which is helpful in rehabilitation medicine for the designing assistive technologies. The MRE can also encode muscle function via the measurement of viscoelastic properties, but can only be used in a relaxed state (102). Recently, Schrank *et al.* (103) introduced real-time MRE to measure changes in viscoelastic parameters induced in different groups of skeletal muscle of the lower extremities during dynamic exercises. This method provides valuable information for the study of physiological processes and the diagnosis of diseases.

**Emerging trends**

The evolution of keywords reflects the emerging trends in MRE-associated research. From 1995 to 2000, studies focused on the development of MRE technology and preliminary experiences in *ex vivo* tissues, with keywords including "tissue", "magnetic resonance elastography", "acoustic strain wave", "elasticity", "disease", and "reconstruction". From 2001 to 2010, MRE was initially applied to various parts of the body, notably the liver, brain, breast, and skeletal muscle. A high number of research hotspots emerged, with keywords including "in vivo", "MRI", "model", "skeletal muscle", "visualization", "stiffness", "breast lesion", "behavior", "hepatic fibrosis", "noninvasive assessment", "biopsy", "portal hypertension", "brain", "hepatic steatosis", and "hepatocellular carcinoma". Since 2011, the MRE technique has been optimized and is widely used clinically, and research on MRE has focused on "diagnostic performance", "accuracy", and "repeatability".

**Research frontiers**

From the burst analysis of keywords, the research frontiers between 1995 and 2000 were "tissue", "acoustic strain wave", "displacement", "reconstruction", and "elasticity". These topics were mainly associated with the MRE technique. Between 2001 and 2017, the research frontiers were "skeletal muscle", "visualization", "breast", "breast cancer", "behavior", "liver viscoelasticity", "chronic hepatitis C", "repeatability", "liver stiffness measurement", "healthy volunteer", and "clinical application". These topics focused on the clinical application of MRE in various organs. In recent years, the research frontiers have included "diagnostic performance", "diagnostic accuracy", "hepatic steatosis", "chronic hepatitis B", "radiation force impulse", "children", "elastography", and "echo".

Many aspects of MRE have yet to be studied. First, unlike the case of liver MRE and the staging of fibrosis, many organs lack a standardized MRE protocol and agreement regarding baseline values in healthy individuals. Second, most MRE applications have focused on disease diagnosis, and recent studies have shifted towards monitoring treatment with neoadjuvant chemotherapy, predicting the risk of malignancy, and even disease prevention. Studies have shown that tumor stromal pressure and collagen changes may reflect the response to therapy (104,105), and more advanced MRE methods are needed to evaluate these microscopic changes. Third, the use of MRE in children is challenging (106). Therefore, it is critical to further develop MRE techniques to measure the mechanical properties of smaller structures more accurately. Current research focused on MRE technology has indicated the need for further improvement with regard to the MR sequence and the mechanical wave generator. These techniques, described by the keywords "echo" and "radiation force impulse", are optimized to increase the "diagnostic performance" and "diagnostic accuracy" of MRE, so that it can be better used in "hepatic steatosis", "chronic hepatitis B", and "children".

### *Limitations*

This study had several limitations. First, only the WoSCC database was searched for research data. Certain literature studies were not included, which could have resulted in a significant sample size error. Second, only studies published in English were included, and those published in other languages were excluded, which may have caused language bias. Third, we focused mainly on MRE in humans and not animal experiments, so most studies involving animals were filtered out. A further limitation of this study is that authorship in relation to commercial contracts was not considered.

 

## Conclusions

Scientometric and visualization analysis in MRE can provide information regarding the knowledge framework, research hotspots, frontier areas, and emerging trends in this field.

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## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-207/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Due to the literature review design of the present study, neither ethics approval nor informed consent was applicable.



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## Appendix 1: brief introduction to history of MRE technology development and clinical application

### *History of technology development*

Parker (13), as the elastography pioneer, firstly imaged the biomechanical properties of tissue using ultrasound elastography. From then, the field of "imaging the elastic properties of tissues" has been expanding rapidly in imaging modalities including MRE over the last 30 years.

**Actuator**

- ❖ In 1995, the electromagnetic vibration device was designed by Muthupillai *et al.* to generate waves in agar gel (61).
- ❖ In 1999, Rossman *et al.* (107) developed an electromagnetic vibration device for mechanical excitation of the human.
- ❖ 1n 2003, Braun *et al.* (108) designed an electromagnetic actuator for generating variably oriented shear waves.
- ❖ In 2003, Doyley *et al.* (63) developed a piezoelectric actuator applied inside the diameter spherical imaging volume.
- ❖ In 2006, Chan *et al.* (109) developed a needle-based shear wave generator with piezoelectric bending elements to instead of a long piezoelectric stack. The wave propagation in a target region has a well-defined shape with longitudinal motion of around 200mm, reducing orientation-related error in the wavelength estimation in application of surface drivers.
- ❖ In 2006, Sinkus *et al.* (110) used aortic valve closure as internal driver to generate shear wave for measuring the shear modulus of the interventricular septum.
- ❖ In 2008, Talwalkar *et al.* (111) developed a system for MRE examination of the liver, in which a loudspeaker and a passive driver was connected by a pneumatic tube.
- ❖ In 2011, a design concept with piezoelectric stack was developed by Claton *et al.* (64) to generate high-frequency vibrations for small-animal brain MRE studies over a broad range of driving frequencies, from 600-1800Hz.
- ❖ In 2011, Murphy MC *et al.* (94) used the soft pillow driver for 3D brain MRE and verified the soft vibration source was reliable and comfortable.
- ❖ 1n 2018, Guertler *et al.* (65) designed a custom multi-directional jaw actuator to transmit vibrations from a pneumatic driver into the mini-pig brain for direct estimates of brain mechanical properties.
- ❖ In 2019, Huang X *et al.* (112) designed an ergonomic pillow-like passive driver for brain MRE.

**MR sequence and imaging strategies**

- ❖ In 1989, the first MR elasticity experiment was conducted using 1.5T MR system (General Electric, Milwaukee) with a standard spin echo sequence by R. Buxton and A. Sarvazyan at the University of California at San Diego (113).
- ❖ In 1992, MR elastography studies with static loading of tissue mimicking phantoms were conducted at the University of Michigan-Ann Arbor (114).
- ❖ In 1995, propagation of the shear wave in the homogeneous phantom was recorded by MR imaging in the University of Michigan and Artann Laboratories (115).
- ❖ In 1996, Muthupillai R (116) developed a modified phase contrast gradient echo sequence for motion-sensitizing cyclic gradient waveforms. In 2006, Maderwald S *et al.* (83) designed a multiecho phase-contrast gradient echo sequence to accelerate MRE acquisitions.
- ❖ In 2002-2003, Braun J *et al.* (68) and Weaver JB *et al.* (117) respectively used a single shot echo planar imaging (EPI) with spin-echo sequence and gradient-echo sequence to accelerate the scan time. In 2006, Kruse SA *et al.* (69) studied the mechanical properties of the brain using fast EPI based 3D MRE.
- ❖ In 2006, Klatt D *et al.* (70) combined steady-state free precession sequence with fractional MRE for rapid measurement of liver stiffness in vivo.
- ❖ In 2007 Rump J *et al.* (84) introduced fractional MRE, in which the motion encoding gradient with duration shorter than the vibration period was utilized for fractional encoding of harmonic motions. Soon after, Klatt D *et al.* (85) developed a multifrequency MRE for the simultaneous acquisition of multifrequency vibrations along one spatial dimension within one temporally resolved MRE experiment.
- ❖ In 2013, Klatt *et al.* (86) developed sample interval modulation-MRE to improve MRE efficiency and shorten the acquisition time. MEG along 3 encoding directions with different starting time was performed to simultaneously encode 3-directional tissue displacement into the phase of MR signal. Then displacement information at each encoding direction can be fully recovered from harmonics to calculate stiffness using Fourier transform on the phase offset.
- ❖ In 2014, Yin *et al.* (87) proposed a diffusion-MRE technique in which MRE and diffusion-weighted

imaging images were simultaneously acquired to provide complementary information about tissue mechanical properties and structural characteristics. In 2017, Yin *et al.* (88) expended this technique to perform DTI and MRE simultaneously.

- ❖ In order to accelerate the acquisition time, Ahmad *et al.* (89) in 2016 proposed a compressed sensing MRE, in which utilized composite regularization with a constant magnitude to recover phase images for estimating the stiffness, and in 2017, Guenthner *et al.* (90) developed a simultaneous multislice MRE technique, largely relies on the total number of receiver coils available and their complex sensitivity profiles.
- ❖ In 2021, Xi *et al.* (71) used spiral staircase for 3D brain MRE.
- ❖ Multifrequency MRE (tomoelastography) (k-MDEV algorithm), a milestone within the MRE community, was invented by Tzschätzsch *et al.* (91). This method results in compound maps of wave speed, which reveal variations in tissue elasticity in a tomographic fashion. Three models including Voigt, Maxwell and spring-pot models are commonly used, especially the spring-pot model with better representing soft-tissue behavior in the frequency range of MRE (118).

**Inversion algorithm**

- ❖ Local frequency estimation invented by Knutsson *et al.* (119) in 1994 is the basis of the commercial MRE from Resoundant. This inversion algorithm calculates only local wavelength or wave speed.
- ❖ Linear inversion solves a linear minimization problem by assuming that stiffness variables as the unknowns are linearly dependent. This method results overdetermined matrix system, which is solved by least-squares matrix inversion. Manduca A *et al.* (120) in 1996 presented a local frequency estimation, which utilizes the local spatial frequency of shear waves to estimate the shear modulus via a wave velocity equation under assumptions of local homogeneity and incompressibilty. This method is suitable for regions where the elastic properties do not vary significantly. In 2007, Rouviere O *et al.* (49) introduced a local direct inversion, which utilizes the curl operator to eliminate the compressional component and the unknown shear modulus is estimated directly from measurement data via direct inversion of a Helmholtz-like equation with a local homogeneity assumption.
- ❖ Nonlinear inversion was initially developed by Van Houten *et al.* (121) in 1999 to improve the estimations for elastography maps of viscoelastic or poroelastic parameters via solving a nonlinear constrained minimization problem. This method only considers displacement fields that satisfy the governing equations. Therefore, it is strongly dependent on model assumptions such as initial stiffness values and boundary conditions.
- ❖ In 2018, Murphy MC *et al.* (122) used artificial neural networks to inversion of MRE data to estimate stiffness.

### *History of clinical application*

**Liver**

- ❖ MRE was originally developed for liver imaging (49). In 2006, Huwart *et al.* (123) initially studied the feasibility of MRE for determining the stage of liver fibrosis. In 2007, Yin M *et al.* (124) obtained preliminary estimates of the sensitivity and specificity of the MRE in diagnosing liver fibrosis. Their results provided continued motivation for further evaluation of hepatic MRE in patients with suspected hepatic fibrosis. In 2016, Meissner *et al.* (125) used MRE to assess the treatment response in HIV and HCV patients with simtuzumab.
- ❖ In 2009, Talwalkar *et al.* (126) performed a preliminary study on measuring spleen stiffness in patients with chronic liver disease and found that portal hypertension increased the stiffness of liver and spleen. They concluded that MRE could be used as a quantitative method for predicting the presence of esophageal varices in patients with advanced hepatic fibrosis.
- ❖ In 2008, Venkatesh *et al.* (127) performed a study including 44 patients with benign or malignant tumors. The preliminary results showed that malignant tumors were stiffer than healthy liver and benign tumors similar with the healthy liver. In 2017, Thompson *et al.* (128) assessed tumor aggressiveness with MRE and found the stiffness of poorly differentiated hepatocellular carcinomas was significantly lower than well/moderately differentiated hepatocellular carcinomas. In 2019, Shahryari *et al.* (129) applied tomoelastography to map quantitatively the solid-fluid tissue properties of soft tissues and found that tomoelastography could distinguish between benign and malignant liver lesions with high sensitivity based on stiffness.
- ❖ In 2014, Chen *et al.* (130) used MRE to assess treatment response with laser ablation. In 2017, Gordic *et al.* (131)


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evaluated the efficacy of yttrium radioembolization in patients with hepatocellular carcinomas. In 2021, Marticorena Garcia *et al.* (132) used tomoelastography to longitudinally evaluate viscoelasticity changes in the liver and in renal allografts after direct-acting antiviral treatment in kidney transplant recipients with chronic hepatitis C virus infection and suggested that tomoelastography can be used to monitor the therapeutic results of HCV treatment based on hepatic and renal viscoelastic parameters.

**Breast**

- ❖ In 1998, Lawrence *et al.* (133) initially reported the MRE technique for the breast in healthy volunteers and demonstrated that the shear modulus of glandular tissue was 4- to 7-fold higher than the fat.
- ❖ In 2003, Lorenzen *et al.* (134) studied the changes of shear modulus in fibroglandular tissue based on menstrual cycle with MRE and revealed significantly periodic changes.
- ❖ In 2002, Lorenzen *et al.* (135) performed a preliminary study with MRE in patients with neoplasms and demonstrated that malignant lesions had a mean elasticity much higher than benign lesions. In 2007, Sinkus *et al.* (136) found that malignant lesions with more aggressive features may exhibit more liquid-like behavior. In 2018, Balleyguier *et al.* (137) found that the phase angle was an important parameter in predicting malignancy.

**Kidney**

- ❖ In 2011, Rouviere *et al.* (138) evaluated the feasibility and the reproducibility of renal MRE in healthy volunteers. In 2012, Lee *et al.* (139) demonstrated the feasibility of MRE on renal transplant and supported known multifactorial influences on renal stiffness. In 2016, Marticorena Garcia *et al.* (140) confirmed that renal stiffness was significantly lower in recipients with nonfunctioning transplant using multifrequency magnetic resonance elastography.
- ❖ In 2018, Prezzi *et al.* (141) explored the feasibility of MRE for characterizing indeterminate small renal tumors and found that the viscoelastic parameters had diagnostic potential for distinguishing renal oncocytoma from clear-cell renal cell carcinomas.
- ❖ In 2018, Marticorena Garcia *et al.* (142) applied tomoelastography to measure normal renal stiffness in adults and found that this modality could provide full field of view maps of renal stiffness with highly detailed resolution. In 2019, Marticorena Garcia *et al.* (143) first performed renal subregional analysis for the medulla, inner cortex, and outer cortex in patients with lupus nephritis using tomoelastography and compared with other MR modalities. They summarized that tomoelastography can be used to detect the nephropathy in patients with lupus nephritis and had a better diagnostic performance than BOLD and DWI. In the same year, Lang *et al.* (144) evaluated renal stiffness changes in patients with IgA nephropathy using tomoelastography and further confirmed that this modality had high diagnostic accuracy for IgA nephropathy and positively correlated with estimated glomerular filtration rate.

**Pancreas**

- ❖ In 2015, Shi *et al.* (145) evaluated the feasibility of 3D MRE to determine the stiffness of the pancreas in healthy volunteers. The results showed that 3D pancreatic MRE provided promising and stable stiffness measurements throughout the pancreas. In 2018, Wang *et al.* (146) certified some predictive accuracy of MRE in detecting and classifying chronic pancreatitis.
- ❖ In 2019, Serai *et al.* (147) studied the feasibility of MRE in pediatric patients and found that stiffness in patients with acute recurrent pancreatitis or chronic pancreatitis decreased comparing to healthy controls.
- ❖ In 2020, Marticorena Garcia *et al.* (148) performed subregional analysis of pancreatic head, body and tail with tomoelastography in patients with pancreatic ductal adenocarcinoma and found that tomoelastography provided a quantitative imaging marker for tissue stiffness depicting pancreatic ductal adenocarcinoma boundaries. In 2021, Zhu *et al.* (149) investigated the stiffness and fluidity of pancreatic ductal adenocarcinoma and autoimmune pancreatitis with tomoelastography and made a conclusion that both pancreatic stiffness and fluidity can be used to differentiate between pancreatic ductal adenocarcinoma and autoimmune pancreatitis with high accuracy. Gültekin *et al.* (150) used tomoelastography to assess the prediction of tumor aggressiveness in patients with pancreatic neuroendocrine tumor and confirmed that tomoelastography could predict the greater tumor aggressiveness by increased stiffness and was positively correlated with PET derived asphericity.


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**Brain**

- ❖ In 2008, Kruse SA *et al.* (151) used MRE to obtain estimates of the shear modulus of human cerebral tissue in healthy adult volunteers. In 2013, Murphy *et al.* (152) measured the characteristic topography of brain stiffness with MRE and found that test-retest repeatability with errors of 1% for global stiffness and 2% for stiffness in the lobes of the brain. In 2016, Johnson *et al.* (99) reported that the repeatability error in measuring stiffness in subcortical gray matter was 3-7%. In 2019, Yeung J *et al.* (153) performed study with multifrequency MRE to characterize the brain tissue stiffness in children compared with adults.
- ❖ In 2010, Wuerfel *et al.* (58) first applied MRE to measure the brain stiffness in a disease state and showed brain stiffness was decreased in patients with MS compared with age-matched controls. In 2011, Murphy *et al.* (154) performed MRE studies focused on neurodegenerative disease and reported the similar results in subjects with Alzheimer disease. In 2017, Elsheikh *et al.* (155) compared brain stiffness changes in 4 classes of dementia with MRE and demonstrated stiffness changes in different regions.
- ❖ In 2007, Xu *et al.* (156) first introduced MRE to assess intracranial tumor's stiffness and showed large variability in viscoelasticity. In order to explore the adherence of the tumor to the surrounding tissue, Yin *et al.* (157) developed a MRE-based slip interface imaging for evaluation of vestibular schwannomas in 2015, based on the assumption that a discontinuity will be created when a shear wave propagate across the boundary.

**Prostate**

- ❖ In 2004, Kemper *et al.* (158) initially assessed the technical feasibility of *in vivo* MRE of the prostate gland and acquired a successful MR data.
- ❖ In 2011, Li *et al.* (159) investigated the feasibility of MRE in the diagnosis of prostate cancer at 3.0T and found that the significant differences in stiffness exist between prostate malignant and benign tissues.

**Lung**

- ❖ In 2006, Goss *et al.* (160) performed lung MRE study and provided preliminary evidence that MRE can be used for assessing the regional mechanical properties of the lung. In 2014, Mariappan *et al.* (161) developed a rapid MRE technique to quantify the respiration-dependent shear stiffness of lung parenchyma. The preliminary data demonstrated clinically feasibility.
- ❖ In 2017, Marinelli *et al.* (162) quantitatively assessed the stiffness of pulmonary fibrosis in patients with fibrotic interstitial lung disease and showed that parenchymal shear stiffness was increased compared to healthy volunteers at both residual volume and total lung capacity.

**Heart**

- ❖ In 2008, Elgeti *et al.* (163) investigated the feasibility of MRE for measuring pressure-related left ventricular function parameters and reported similar results with invasively determined left ventricular pressures. In 2014, Elgeti *et al.* (164) used MRE to diagnose myocardial relaxation abnormalities in patients with diastolic dysfunction and found that the decrease in shear-wave amplitudes within the left ventricular region correlated with the severity of diastolic dysfunction.
- ❖ In 2017, Sui *et al.* (33) developed a MRE technique with reduced field of view in healthy volunteers. The results showed reducing ghosting artifacts and improving image quality significantly compared to the conventional full field of view acquisition.

**Vessel**

- ❖ In 2013, Xu *et al.* (165) performed gated cine MRE to assess the mechanical properties of the abdominal aorta wall. The images at different phases of the cardiac cycle were reconstructed from acquired data throughout the cardiac cycle and the differences in aortic wall stiffness between diastole and systole were calculated.

**Muscle**

- ❖ In 2001, Dresner *et al.* (166) used MRE to quantify the changes in stiffness of skeletal muscle with loading *in vivo* and provided a useful method for studying muscle biomechanics.
- ❖ In 2010, Klatt *et al.* (167) developed a multifrequency MRE to investigate the viscoelastic properties of human skeletal muscle in different states of contraction.
- ❖ In 2019, Zonnino *et al.* (168) introduced a multi-muscle MRE to quantify force for each muscle in the forearm during application of isometric wrist torques and laid a foundation for investigating the neuromuscular control of coordinated motor action.
- ❖ In 2019, Schrank *et al.* (103) introduced a real-time MRE to measure the changes of viscoelastic parameters induced in different groups of skeletal muscles of the


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lower extremity during dynamic exercises.

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