



## White Matter Biomarkers - A Review

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### ABSTRACT

Biomarkers are indicators of a disease or the severity of a disease. For example, in the human body, antibodies can be termed as a biomarker. White matter is important to learn for understanding various topics such as the theory of mind, empathy, clinical disorders in terms of neuroscience. White matter can change depending upon traumatic experience. This research is seen as a scoping literature review. In seeking to identify the relevant literature from the past twenty years, we used common databases such as Pubmed, Google Scholars. Searches of the reference list from relevant review articles were also employed to identify further relevant studies. Search items included, 'white matter', 'biomarkers', 'white matter biomarkers', 'biomarkers used in neurology'. The obtained articles were later thoroughly read through and understood. A total of '45' articles have been selected and reviewed in this article. Biomarkers present in white matter help diagnose the various white matter related diseases which can help prevent further stages or increase of the disease. But accurate biomarkers for white matter disease are yet to be found. More research must be done in order to help prevent and treat white matter diseases. This study on white matter biomarkers still does not have an accurate answer and must be discovered in the future. There are many biomarkers that can serve for white matter, but none of them fulfils the desired features of a biomarker needed for diagnosing white matter diseases. Future studies are to be done for early prevention of diseases related to white matter and its complete use in humanity.



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### INTRODUCTION

Biomarkers are indicators of a disease or the severity of a disease. For example, in the human body, antibodies can be termed as a biomarker (Klein *et al.*, 2018). If we see biomarkers related to coronary heart disease [CAD], an inflammatory biomarker such as fibrinogen or hs-CRP can be used or lipoprotein associated biomarker such as lipoprotein associated PA2 or lipoprotein a and even cystatin C which is an organ specific biomarker can be used. But an ideal biomarker for CAD is still yet to be found (Rusnak, 2017; Klein *et al.*, 2018). In the

case of aging or age-related diseases, Micro RNAs, can be used which are detected by microarray and sequencing, and various other techniques (Kumar *et al.*, 2017).

White matter is important to learn for understanding various topics such as the theory of mind. Empathy, clinical disorders in terms of neuroscience (Wang and Olson, 2018). It was noticed that white matter changes, but this change depends upon various traumatic experiences (Siehl *et al.*, 2018). Human behaviour can be changed if the white matter tract is distributed [in terms of cognition] (Filley and Fields, 2016).

In an article written by Hansen, they had mentioned that white matter tract integrity [WMTI] biomarkers show promising results in brain development studies. Still, currently, it is being used only in animal studies and slow progressing studies. The fast approach of WMTI can be used in pre-clinical trials and research before being used on patients (Hansen *et al.*, 2017). Cerebrospinal fluid [CSF] biomarkers had also been used to detect white matter lesions. But this research showed lack of association between white matter lesions and Alzheimer's disease [AD] in terms of CSF biomarkers (Jonsson *et al.*, 2010; Bjerke *et al.*, 2014). In another research article, it was found that white matter hyperintensities [WMH] played the role of biomarkers in cerebrovascular diseases [CVD] (Chutinet and Rost, 2014).

Over the past years various research done by our team was on Osteology (Choudhari and Thenmozhi, 2016; Hafeez and Thenmozhi, 2016), stature estimation (Krishna and Babu, 2016), uses and ill effects of electronic gadgets (Sriram *et al.*, 2015; Thejeswar and Thenmozhi, 2015), on RNA (Johnson *et al.*, 2020; Sekar *et al.*, 2019), animal studies (Seppan *et al.*, 2018) and in few other fields (Menon and Thenmozhi, 2016; Samuel and Thenmozhi, 2015). There is a lack of information on the current topic of white matter biomarkers, hence the main aim of this study is to explore and review some detailed information on white matter biomarkers and its related topics (Subashri and Thenmozhi, 2016).

## MATERIALS AND METHODS

This research is seen as a scoping literature review. In seeking to identify the relevant literature from the past twenty years, we used common databases such as Pubmed, Google Scholars (Kannan and Thenmozhi, 2016; Keerthana and Thenmozhi, 2016). Searches of the reference list from relevant review articles were also employed to identify further relevant studies. Search items included, 'white matter', 'biomarkers', 'white matter biomarkers', 'biomark-

ers used in neurology'. The obtained articles were later thoroughly read through and understood. A total of '45' articles have been selected and reviewed in this article (Pratha and Thenmozhi, 2016; Nandhini *et al.*, 2018). Quality of articles used was assessed using a quality assessment tool and graded as strong, moderate and weak.

## Biomarkers

### Acute Kidney Injury

Acute kidney injury [AKI] occurs usually based on serum creatinine change. Diagnosis of AKI, this was studied in a total of 31 studies, from which 25 studies out of the 31 studies had good quality. From these studies, it was found that serum cystatin C, urine IL-18 and urine KIM-1 gave better results for the diagnosis of AKI.

These biomarkers have great potential but need more future study (Coca *et al.*, 2008). Often in the case of AKI, renal replacement therapy [RRT]. But there is one problem, ideal circumstances of whether to or whether not to do this therapy is still unclear. In this study, a total of 63 studies was performed on 15,928 critically ill patients.

Through this study, several biomarkers showed promising results, but this current evidence is not enough to prove the establishment of these biomarkers for clinical purposes (Hansen *et al.*, 2017).

### Micro RNAs

Micro RNAs [Mi RNAs] are important regulators. In this research article, they have mentioned that Mi RNAs have great potential to be biomarkers for prostate cancer management. But this review does not show any promising results and thus, more research and future clinical studies must be done (Fabris *et al.*, 2016). As seen in the introduction, Mi RNAs are found in biofluids [circulating].

Mi RNAs can act as a biomarker for aging and age related diseases. Mi RNAs are quite suitable in circulation and are detected by microarray and sequencing [a high-throughput technique] (Kumar *et al.*, 2017).

### Coronary Heart Disease

Coronary heart disease [CAD] is one of the most common reasons of death all around the world. Various biomarkers such as fibrinogen, lipid associated biomarkers and organ specific biomarkers have been used in this research article.

These biomarkers fulfilled several qualities of an ideal biomarker for CAD. But none fulfilled all the qualities desired, hence further study is needed for this research (Rusnak, 2017).

### Osteoarthritis

Several protein and non protein biomarkers have been found to diagnose osteoarthritis. But the improved quality of sample and testing, as well as more clinical trials are needed as they may help in identifying a suitable biomarker which may fulfil all the requirements of an ideal biomarker for osteoarthritis (Watt, 2018).

### Neonatal Sepsis

There are many biomarkers such as CRP and PCT, but both have not fulfilled the ideal qualities of a biomarker for neonatal sepsis. Further study must be done so that with the help of the biomarker, neonatal sepsis can be identified in an early stage and appropriate measures can be taken (Sharma et al., 2018).

### White Matter

White matter diseases are poorly understood. For understanding the radiological manifestations, we must understand the pathological view. Few of the previous research articles had made a systematic approach to the radiological findings (Sarbu et al., 2016). In another research article, white matter degeneration is related to vascular dementia and other age related diseases. It was also mentioned in this research that the preservation of axonal function and prevention of cognitive impairment is very important (Hase et al., 2018). The association between white matter and cognition has shown a lot of new scopes. But many are there to be discovered as one can face many challenges while trying for new opportunities (Filley and Fields, 2016).

In a research article, it was seen that out of 792 cases, there were several cases which proved the association between neuroinflammation and white matter pathology in people with schizophrenia (Najjar and Pearlman, 2015). It is also important to understand white matter injury and also its recovery after a hypersensitive intracerebral haemorrhage (Zuo et al., 2017). It was also found that the white matter is damaged in early treated phenylketonuria [ETPKU] patients. But this study also did not show proper evidence and had poor control in various studies (González et al., 2018).

### Neurology

Biomarkers used in neurology are in need of greater study, to help in early diagnosis of CNS conditions. In an article, it was found out that saliva was used as a biomaterial, it is an alternative and also has several advantages. Its use has been studied from many perspectives and can also become an actual biomarker (Wormwood et al., 2015). Psychiatric disorders are disturbances of cognitive functions.

The benefits of neurosciences and biomarkers can help solve mysteries of multiple regions of the brain, along with various features (Wang and Olson, 2018; Lydon-Staley and Bassett, 2018). Computational neuroscience or psychiatry developments can allow simultaneous diagnosis as well as treatment of mental disorders using techniques such as neuroimaging, etc (Yahata et al., 2017).

### White Matter Biomarkers

There are several white matter tract integrity biomarkers which showed promising results. When an axially symmetric diffusion kurtosis imaging [DKI] and conventional DKI were compared with each other, axially symmetric DKI showed faster protocols which may be useful for preclinical research (Hansen et al., 2017). A continuous theta burst stimulation [cTBS] advanced the knowledge of white matter and showed different relations in individuals with stroke (Wadden et al., 2019).

### Parkinson'S Disease

Quantitative Susceptibility Mapping [QSM], as well as Diffusion Tensor Imaging, was used to evaluate the white matter alterations. It was seen that both showed similar results. Further combination of QSM and DTI will provide a complete evaluation of the brain's diseased state (Guan et al., 2019). There is not even one clear biomarker which shows promising results for Parkinson's disease. A combinatorial and multimodal approach must be developed in the future (Mehta and Adler, 2016).

### Alzheimer's Disease

It was noticed that A $\beta$ 42 and tau had a lot of chances of becoming a future biomarker in saliva. And it was also noticed that lactoferrin and other selected metabolites also have the potential. Future researches must be done (Gleerup et al., 2019; Olsson et al., 2016). Lipid biomarkers had also shown various roles in being a biomarker for Alzheimer's disease (Zarrouk et al., 2018).

### Dementia

CSF and blood based biomarkers, diagnosed in vivo also showed a lot of potential of a biomarker in various stages of this research (Hort et al., 2010; Ahmed et al., 2014). Different biomarkers showed various relations between aging, dementia and cognition impairment (Jagust et al., 2009).

## RESULTS AND DISCUSSION

Biomarkers present in white matter help diagnose the various white matter related diseases, which can help prevent further stages or increase of the disease is yet to be found (Bjerke et al., 2014).

**Table 1: Quality of study for articles used in review**

S. No	Author	Year	Type of Study	Key Points	Quality of Study
1.	<a href="#">Hansen et al. (2017)</a>	2017	Review	Axially symmetric DKI	Strong
2.	<a href="#">Wadden et al. (2019)</a>	2019	Review	cTBS	Moderate
3.	<a href="#">Chutinet and Rost (2014)</a>	2014	Review	Cerebrovascular disease	Moderate
4.	<a href="#">Bjerke et al. (2014)</a>	2014	Review	Cerebrovascular biomarker	Strong
5.	<a href="#">Guan et al. (2019)</a>	2019	Review	Parkinson's disease	Moderate
6.	<a href="#">Rusnak (2017)</a>	2017	Review	Biomarker- CAD	Strong
7.	<a href="#">Mehta and Adler (2016)</a>	2016	Review	Parkinson's disease- biomarker	Moderate
8.	<a href="#">Coca et al. (2008)</a>	2008	Review	AKI- biomarker	Moderate
9.	<a href="#">Olsson et al. (2016)</a>	2016	Review	CSF and blood biomarker	Moderate
10.	<a href="#">Watt (2018)</a>	2017	Review	Osteoarthritis biomarker	Strong
11.	<a href="#">Sharma et al. (2018)</a>	2018	Review	Neonatal sepsis	Moderate
12.	<a href="#">Sarbu et al. (2016)</a>	2016	Review	White matter disease	Strong
13.	<a href="#">Hase et al. (2018)</a>	2018	Review	White matter degeneration, dementia	Moderate
14.	<a href="#">Zarrouk et al. (2018)</a>	2018	Review	Lipid biomarker- alzheimer's disease	Moderate
15.	<a href="#">Ahmed et al. (2014)</a>	2014	Review	Dementia- biomarkers	Moderate

Linda and Helena both did research on biomarkers, but both of them stated that they needed a larger and deeper future study for more evidence of the biomarker ([Fabris et al., 2016](#); [Gleerup et al., 2019](#)).

Helena and Bob found quite a few biomarkers for Parkinson's disease. But out of the few selected and analysed, none showed complete efficiency ([Gleerup et al., 2019](#); [Olsson et al., 2016](#)). Maria and Xiaojun used MRI sequences and DTI techniques for diagnoses of white matter diseases ([González et al., 2018](#); [Guan et al., 2019](#)).

Nicolae discussed various white matter diseases in a radiological approach which is poorly understood by many ([Sarbu et al., 2016](#)). Brian and Chutinet found biomarkers, but again none of them fulfilled the criteria and did not have the full potential to be a biomarker for white matter ([Hansen et al., 2017](#); [Coca et al., 2008](#)). Jonsson diagnosed white matter biomarkers using MRI ([Jonsson et al., 2010](#)) while Wadden used cTBS technique for diagnosing white matter biomarkers ([Wadden et al., 2019](#)).

Bob found three biomarkers for Alzheimer's disease. These were systematically reviewed and was found out that it can be used for future clinical use ([Olsson et al., 2016](#)). Maria found cerebrovascular biomarkers such as NF-L, MBP, MMPs. TIMP for diagnosing white matter diseases ([Bjerke et al., 2014](#)).

Few of the limitations which can be seen in this study are that a larger and deeper study is required as well as future studies of discovering white matter biomarkers for recognition of white matter diseases.

There must be more future study done on this topic. The study on white matter biomarkers still does not have an accurate answer and must be discovered.

## CONCLUSION

There are many biomarkers that can serve for white matter, but none of them fulfils the desired features of a biomarker needed for diagnosing white matter diseases. This review concludes that further studies are to be done for early prevention of diseases related to white matter and its complete use in humanity.

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## Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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