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Exploring comorbidity networks in mild traumatic brain injury subjects through graph theory: a traumatic brain injury model systems study

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Abstract

Background Traumatic brain injuries (TBIs) are characterized by myriad comorbidities that affect the functioning of the affected individuals. The comorbidities that TBI subjects experience span a wide range, ranging from psychiatric diseases to those that affect the various systems of the body. This is compounded by the fact that the problems that TBI subjects face could span over an extended period post-primary injury. Further, no drug exists to prevent the spread of secondary injuries after a primary impact.

Methods In this study, we employed graph theory to understand the patterns of comorbidities after mild TBIs. Disease comorbidity networks were constructed for old and young subjects with mild TBIs and a novel clustering algorithm was applied to understand the comorbidity patterns.

Results Upon application of network analysis and the clustering algorithm, we discovered interesting associations between comorbidities in young and old subjects with the condition. Specifically, bipolar disorder was seen as related to cardiovascular comorbidities, a pattern that was observed only in the young subjects. Similar associations between obsessive-compulsive disorder and rheumatoid arthritis were observed in young subjects. Psychiatric comorbidities exhibited differential associations with non-psychiatric comorbidities depending on the age of the cohort.

Conclusion The study results could have implications for effective surveillance and the management of comorbidities post mild TBIs.

Keywords Traumatic brain injuries, Graph theory, Comorbidities, Disease comorbidity network, Centrality

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Background

Traumatic brain injuries (TBIs) are a significant public health concern affecting numerous countries across the globe [1–5]. TBIs are major contributors to fatalities and disabilities and exert a severe influence on the lives of the injured subjects and their family members [1–5]. Further, TBI survivors often have to deal with long-lasting complications that could significantly impact their quality of life and daily functioning [2, 6–9]. The cost of diagnosing, treating TBIs, and managing post-traumatic complications in survivors of the condition could be enormously high, resulting in severe stress on the healthcare systems of the country [1–5]. Hence, a more significant focus and resources should be dedicated to enabling disease prevention.

TBI survivors often experience the development of a wide range of psychiatric and medical comorbidities that severely derail their work life and cognitive functioning [7–10]. These comorbidities are reported in TBIs of all severities, including mild, moderate, and severe forms of the injury [8, 10]. In a study of mild TBI (mTBI) subjects [8], the authors quantified the prevalence of psychiatric and medical comorbidities at five years post-injury and as a function of the biological sex and age of the subjects. Mild TBI survivors are prone to developing highly diverse comorbidities ranging from cardiovascular, neurologic, and respiratory to psychiatric [8, 11–14]. Similar results have also been reported after severe and moderate impacts to the brain [10].

The complications and comorbidities that TBI survivors develop after an impact on the brain can be attributed to primary and secondary brain injuries [2, 15]. While primary injuries often happen immediately after an impact on the brain, the timescale of secondary brain injuries can vary from hours after the impact to days, months, and potentially years after the primary impact [2, 15, 16]. The primary injuries that damage local neurons, glia, and blood vessels are often irreversible [2, 15, 16]. On the other hand, the pathophysiological mechanisms guiding the development and subsequent spread of secondary brain injuries could be halted by applying numerous therapeutic strategies [15–17]. Unfortunately, despite the concerted efforts by the TBI community in search of a potential therapeutic agent to prevent the cascade of secondary brain injuries, no clinical trials have been successful so far in humans [18–22]. Even though numerous drugs have shown superior efficacy in preventing secondary injuries in animal models of TBIs, such an effect was not observed in human clinical trials [19, 20].

When successful treatment options don't exist to treat the condition [18–20], the focus should be on the careful management of comorbidities for effective patient care [2, 23, 24]. However, continued surveillance of TBI survivors for all possible sets of comorbidities is impractical due to the associated costs and the wide range of comorbidities that TBI survivors often develop over a very long period following a primary impact [2, 7–10]. The heterogeneous nature of TBI injury types also complicates the situation [25, 26]. TBIs are considered very heterogeneous owing to several factors, and it is widely expected that heterogeneous injuries could give rise to diverse patterns in the development of comorbidities over time [25, 26]. Hence, a more practical and economical way to monitor comorbidities in TBI subjects is required to avoid injury-associated complications [27].

In this study, we propose applying the principles of graph theory to decipher distinct patterns in the development of comorbidities after mild TBIs [27]. We analysed mTBI subjects five years post-injury using the Traumatic Brain Injury Model Systems National Database (TBIMS) data [28]. By utilizing the data in the database [28], we constructed network graphs comprising comorbidities as nodes and edges representing the associations between them [27]. We decided to focus on mTBIs since the field is relatively under-explored, and the diagnosis of comorbidities post the condition goes largely unnoticed [29, 30]. Upon application of various statistical measures and clustering techniques, we uncover unique patterns in the development of post-traumatic comorbidities separately in young and old subjects. Our study yields novel observations in the development of comorbidities post mTBIs that could effectively be utilized for disease prevention and management.

Methods

Our study employs a graph theory approach [27] to investigate patterns of disease co-occurrence following mTBIs (5 years). We leveraged the Traumatic Brain Injury Model Systems (TBIMS) database (http://www.tbindsc.org) [28], a comprehensive database of TBI subjects encompassing vital information about the development of comorbidities. Specifically, we included subjects with mTBIs as determined by the Glasgow Coma Scale (GCS) score ($13 <= GCS <= 15$) [2, 31]. We also restricted our analysis to subjects with five years of follow-up data to capture a sufficient time frame for potential disease co-occurrences to emerge. A request to access the data in the public version of the database [28] was placed in February 2023, and the access was granted subsequently.

The information regarding possible comorbidities (presence, absence, and onset) was collected through the National Health and Nutritional Examination Survey (NHANES) [32]. A total of 26 medical and psychiatric comorbidities were included in our study, which were grouped under the following categories: psychiatric, musculoskeletal and rheumatologic, cardiovascular, respiratory, neurologic, endocrine, gastrointestinal, and ophthalmologic group of comorbidities.

Under psychiatric comorbidities, the following comorbidities were included: Alcoholism, drug addiction (DA), depression, anxiety, obsessive-compulsive disorder (OCD), panic attacks (PA), bipolar disorder (BPD), attention deficit disorder/ attention deficit hyperactivity disorder (ADDADHD), and post-traumatic stress disorder (PTSD). The cardiovascular group of comorbidities had information regarding hypertension, congestive heart failure (CHF), stroke, myocardial infarction (MI), high blood cholesterol (HBC), and other heart conditions (OHC). Sleep disorder (SD), dementia, and movement disorder (MD) were included under the neurologic category. The musculoskeletal and rheumatologic groups include rheumatoid arthritis (RA), osteoarthritis (OA), and chronic pain (CP). Diabetes, cataracts, and liver disease (LD) were included under endocrine, ophthalmologic, and gastrointestinal conditions, respectively.

After filtering the data from the TBIMS database [28], we constructed disease comorbidity networks for all subjects, young ($<=50$ years) and old (>50 years). In the comorbidity network, the 26 diseases represent the nodes, and the edges represent their associations

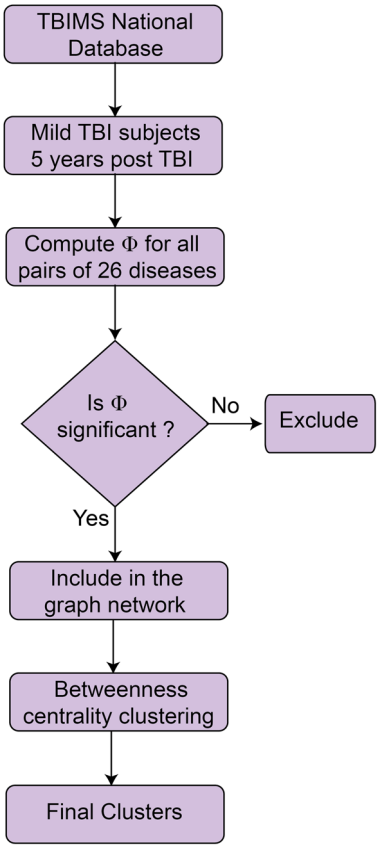

Fig. 1 Schematic workflow of the analysis of disease comorbidity networks in mTBI subjects. Flow chart represents various steps in the construction of disease comorbidity network and subsequent clustering based on betweenness centrality

[33–36]. The strength of association between the nodes in the network was computed by estimating the phi-correlation coefficient (ϕ) between each pair of comorbidities. A statistical test was then employed to eliminate the weaker connections and retain only those statistically significant at $p<0.01$ [37]. The exact statistical procedure for constructing the disease comorbidity network [33], including the computation of the phi-correlation coefficient (ϕ), is explained in detail in Additional file 1: Supplementary Methods.

Once the network was constructed, we computed various centrality measures (degree, betweenness, eigenvector) from all three networks (all subjects, young and old) to identify the network's vital nodes (comorbidities) that influence the flow of information [38–40]. The equations governing the computation of the centrality measures and an intuitive diagrammatic explanation (Additional file 1: Fig. S2-S4) of each are given in detail in Additional file 1: Supplementary Methods. Lastly, we employed a novel clustering algorithm called the 'betweenness centrality clustering algorithm' to identify comorbidity clusters that tend to co-occur in the three networks [41]. The algorithm identifies nodes with high betweenness centrality values and removes them iteratively from the network (Additional file 1: Fig. S5) until a specific threshold is reached [41]. The algorithm then reinstates the link between the removed nodes (Additional file 1: Table S1) and the remaining connected components in the graph, forming localized clusters of comorbidities [41]. The algorithm is explained intuitively in Additional file 1: Supplementary Methods.

Results

We analysed the information in the TBIMS national database [28] to construct a disease comorbidity network of mTBI subjects at 5 years post injury. The total number of mTBI subjects at 5 years post injury is 4915. Altogether, there was information regarding 26 comorbidities, as mentioned in the Methods section (Fig. 1), collected through the NHANES survey [28], the prevalence of which can be seen in a previous study [8].

As a first step, we computed the extent of co-association between the 26 medical and psychiatric comorbidities. To do so, we calculated the phi-correlation coefficient (ϕ) between each pair of comorbidities [33, 34] (Additional file 1: Fig. S1). After performing a statistical test (Additional file 1: Supplementary Methods), we eliminated weaker connections and retained only the statistically significant ones [37] (Fig. 1). The resulting comorbidities and their connections were represented in the form of a graph network where nodes represent the individual comorbidities (node size represents prevalence) and edges represent the strength of the associations in the form of computed ϕ correlations (Fig. 2).

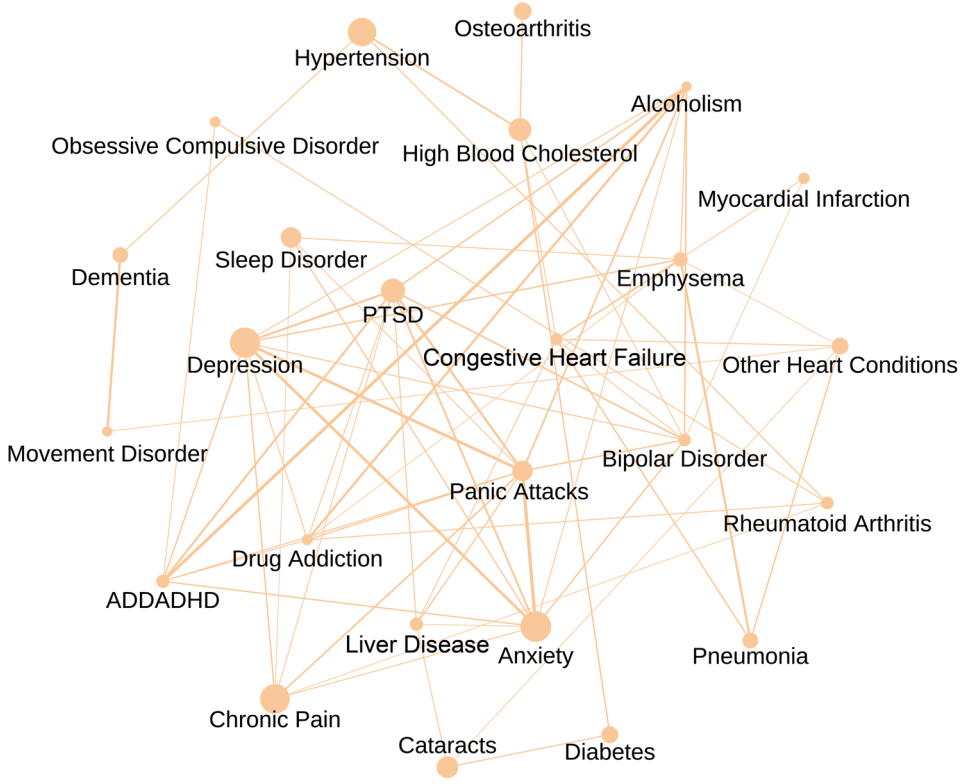

Fig. 2 Disease comorbidity network of all mTBI subjects at 5 years post injury. The nodes in the network represent the comorbidities, while the edges represent associations in the form of phi-correlation coefficient. Node size indicates prevalence, and edge thickness represents the strength of the association

Thicker edges represent stronger connections between comorbidities (Fig. 2). For example, depression exhibits a stronger association with anxiety ($\phi = 0.48$), one of the strongest associations between all sets of comorbidities in the network. On the other hand, chronic pain exhibits a somewhat weaker yet statistically significant connection with anxiety ($\phi = 0.21$). Any isolated comorbidity (stroke) with no connection to other parts of the network was not included (Fig. 2).

To understand the statistical properties of the network and identify vital nodes (comorbidities), we computed various centrality measures [33, 38, 39]. Three vital centrality measures were considered: betweenness centrality, degree centrality, and eigenvector centrality [39] (Additional file 1: Supplementary Methods). All centrality measures identify vital nodes that control information flow and transition patterns in the disease comorbidity network [33]. The distribution of the three centrality measures of the network can be seen in Fig. 3. From the figure, it can be seen that the three centrality distributions differ from each other, although a high correlation can be seen between degree vs. eigenvector centralities ($r = 0.93$). Since betweenness centrality exhibited the most minor correlation with prevalence ($r = 0.028$), we investigated the network further using this metric.

Next, we decided to study the network at a more granular level by identifying localized clusters of comorbidities after eliminating connections between vital comorbidity hubs. To do so, we incorporated an algorithm based on betweenness centrality previously implemented in a study of disease comorbidities [41]. This approach aims to identify comorbidities that occur in close association with each other, which would further help understand their shared physiological mechanisms.

Comorbidity clusters in mTBI subjects

We identified six clusters (Fig. 4) after applying the clustering method based on betweenness centrality [41]. The six clusters differed concerning the constituent nodes and connectivity between them. The first cluster (Fig. 4) includes psychiatric conditions and their connections. The psychiatric conditions found in cluster 1 include PTSD, BPD, ADDADHD, PA, DA, alcoholism, anxiety, and depression (Fig. 4). In addition to observing connections among psychiatric conditions, cluster 1 also encompasses connections between non-psychiatric and psychiatric conditions (Fig. 4). The non-psychiatric conditions seen in cluster 1 include LD, RA, CP, SD, and emphysema. Mainly, emphysema is associated with depression, alcoholism, and DA. One salient point is that

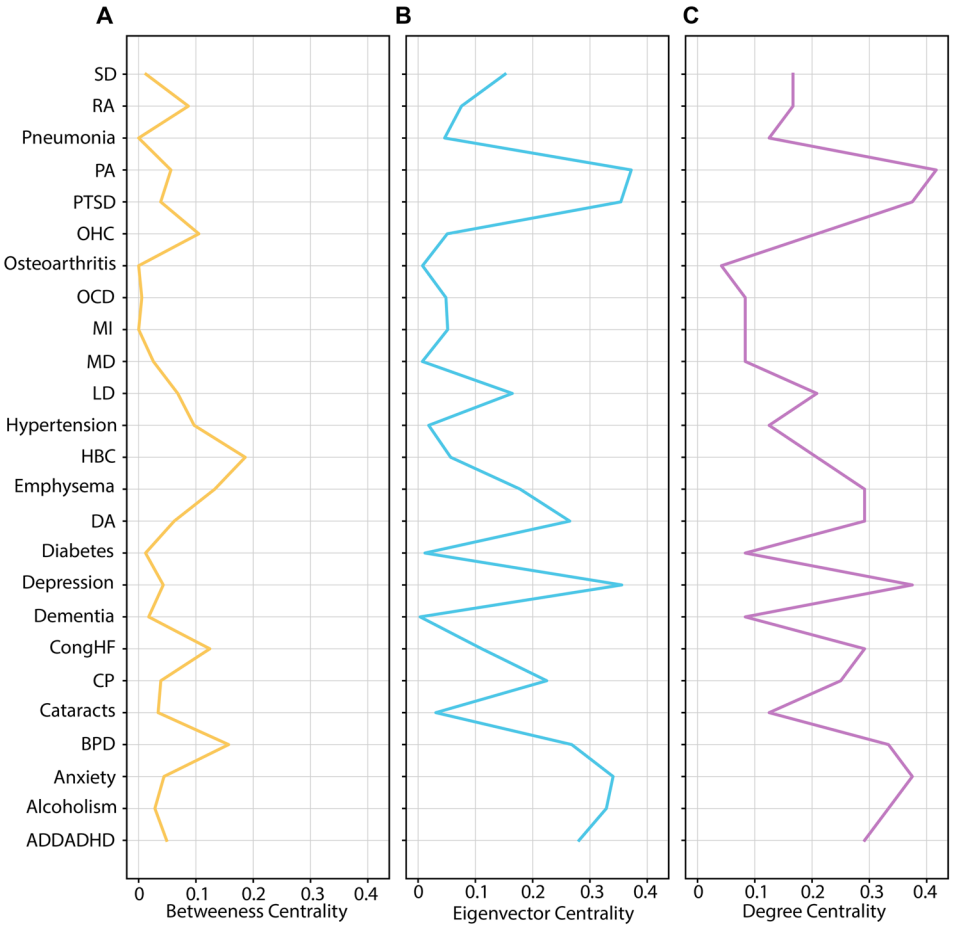

Fig. 3 Distribution of three centrality measures constructed from the comorbidity network of all mTBI subjects. Panel A represents the distribution of betweenness centrality, panel B represents degree centrality, and panel C represent eigenvector centrality

OCD is not associated with other psychiatric conditions in the network (except ADDADHD in cluster 3). Altogether, the first cluster seems to reinforce the fact that psychiatric conditions exhibit a high degree of comorbidity [6–8].

In the second cluster (Fig. 4), diabetes and cataracts are associated with each other and other cardiovascular conditions. Diabetes is comorbid with HBC, and cataracts with OHC. In addition, cataracts, an ophthalmologic condition, is associated with LD. The third cluster (Fig. 4) consists of three constituents: OCD, ADDADHD, and RA. OCD, a psychiatric condition, is associated with both RA and ADDADHD. In the fourth cluster, one can witness the association between cardiovascular comorbidities and other groups of comorbidities. Cardiovascular comorbidities (CHF, OHC) in the cluster are associated with pulmonary comorbidities (pneumonia and emphysema). CHF is, in particular, comorbid with HBC, OHC, MI, LD, BPD, pneumonia, and emphysema. Lastly, BPD is associated with cardiovascular conditions CHF and MI.

In cluster 5 (Fig. 4), one can see the association between neurologic and cardiovascular conditions. In particular, dementia is associated with hypertension, and MD is linked with OHC. Cluster 5 (Fig. 4) also witnesses the association between MD and dementia, RA and HBC with hypertension. Lastly, an association between OA and HBC can be seen in cluster 6. In the next section, we will discuss which associations are seen in young and old mTBI subjects.

Comorbidity clusters in old and young mTBI subjects

As a next step in the study, we examined which comorbidity patterns are observed in old and young subjects. Subjects were categorized as old if their age was greater than 50 years at follow-up (or young otherwise). Similar to the analysis involving all mTBI subjects, we computed the ϕ for all pairs of 26 comorbidities of mTBI subjects (>50 years of age) (Fig. 1). After retaining the statistically significant associations [37], we displayed the information as a network graph (Fig. 5) for old mTBI subjects. Note that stroke, MI, OA, and hypertension were excluded since they are not connected to the

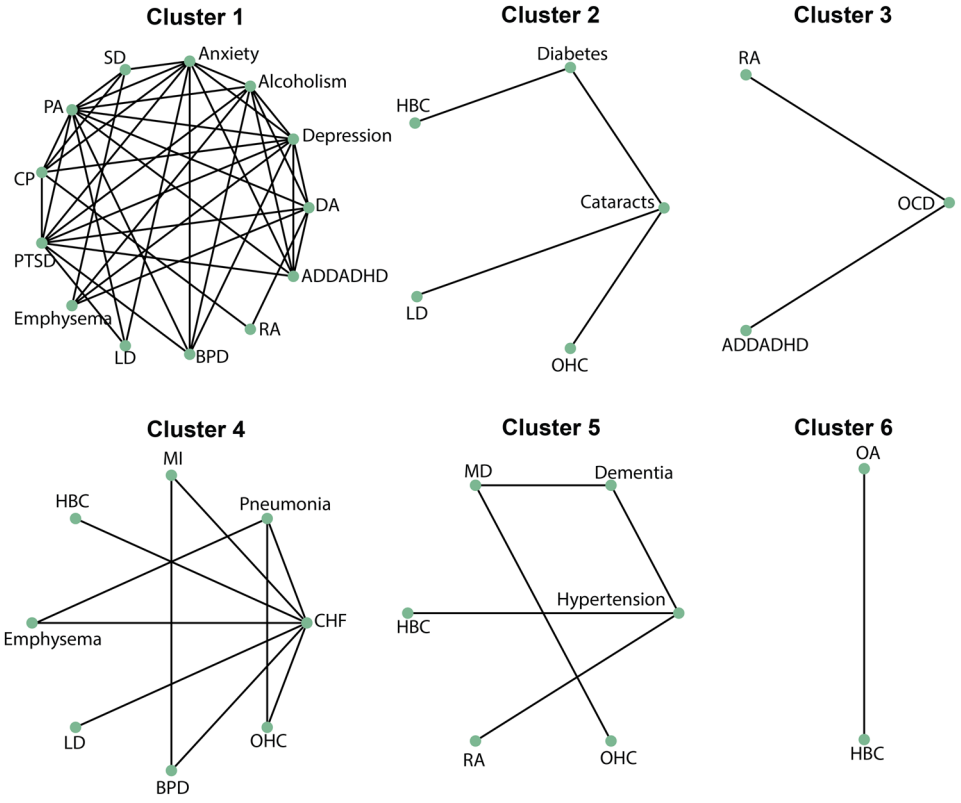

Fig. 4 Application of betweenness centrality-based clustering to the comorbidity network of all mTBI subjects. Individual clusters encompass nodes and edges that represent the comorbidity and the association between them, respectively

leading network. With this network in place (Fig. 5), we applied the betweenness centrality clustering algorithm [41] to identify localized clusters of comorbidities in the network.

First, we found that psychiatric conditions have a high degree of co-occurrence among each other, similar to the results observed in the previous section (Fig. 6). This can be seen from cluster 1 (Fig. 6), where depression, anxiety, PTSD, DA, alcoholism, PA, and BPD tend to be co-associated with each other. In addition to co-occurrence within the group, psychiatric comorbidities are also associated with other somatic conditions. For example, CP is seen to be associated with DA, PA, and PTSD (cluster 1), while RA is associated with DA (cluster 1) and emphysema with depression (cluster 2, Fig. 6). One can also witness co-association between CHF and pulmonary comorbidities (pneumonia and emphysema) in cluster 2 (Fig. 6). Cluster 3 showcases the connection between dementia and MD, typically occurring as people age. Cluster 5 encompasses connections between OCD with diabetes and SD, while Cluster 4 depicts the link between diabetes and HBC (Fig. 6). Lastly, one can see that LD is associated with cataracts and diabetes in cluster 6. The list of removed nodes as a result of applying the clustering algorithm can be seen in the Additional file 1: Table S1.

Next, we performed the same analysis for young mTBI subjects. After constructing the disease comorbidity network for this study group (Fig. 7), we formed localized clusters by applying the clustering algorithm based on betweenness centrality as before. This resulted in seven clusters, as shown in Fig. 8. Similar to the trends seen in older subjects, psychiatric comorbidities tend to co-occur (Fig. 8). This can be seen across cluster 1 and in clusters 2 and 4, where anxiety (cluster 2) and PTSD (cluster 4) were connected to other psychiatric conditions, respectively (Fig. 8). Psychiatric comorbidities were also associated with other somatic diseases like emphysema (cluster 1), LD (clusters 2 and 4), and stroke (cluster 4) (Fig. 8). We also observed a close association between BPD and cardiovascular comorbidities (cluster 3, MI, CHF, HBC). Cluster 5 (Fig. 8) encompasses associations between OCD with RA and ADDADHD. Lastly, we observed that SD is associated with cardiovascular comorbidities (OHC, stroke) and CP (cluster 6).

Next, we identified prominent comorbidity patterns in the network clusters of all subjects (Figs. 2 and 4). We examined whether they were observed in the network of young and old subjects (Figs. 6 and 8, respectively). The features are listed in Table 1, along with the information on whether they are observed in young vs. old cohorts. The analysis revealed some striking similarities and

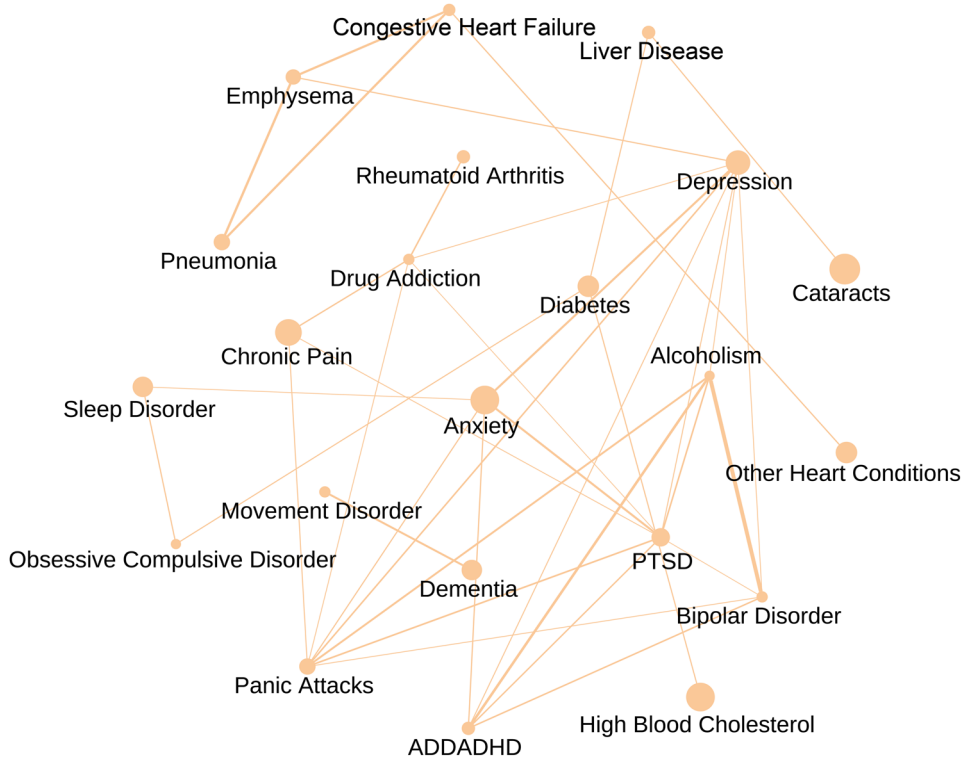

Fig. 5 Disease comorbidity network of old mTBI subjects at 5 years post injury. The nodes in the network represent the comorbidities, while the edges represent associations in the form of phi-correlation coefficient. Node size indicates prevalence, and edge thickness represents the strength of the association

dissimilarities regarding the co-occurrence of comorbidities between the two cohorts (Table 1). Both cohorts were characterized by solid co-occurrences of psychiatric comorbidities. However, the co-occurrence of psychiatric comorbidities with LD was seen only in the young cohort. Similarly, the co-occurrence of psychiatric comorbidities with CP was witnessed only in the old cohort (Table 1). One remarkable feature of the disease comorbidity pattern in the young cohort is that OCD tends to co-occur with ADDADHD and RA (Table 1). In comparison, this association was not present in the old cohort. Cardiovascular comorbidities were associated with other groups of comorbidities in both young and old cohorts, but some differences were also noticed. The association of cardiovascular comorbidities with BPD was seen only in the young cohort (Table 1). The implications of these relative associations in young vs. old cohorts are explained in the discussion section.

Discussion

In this study, we adopted a novel approach of employing graph theoretical principles [27, 33, 42] to identify comorbidity patterns in mTBI subjects. We analyzed the data about mTBI subjects from the TBIMS national database [28] five years after the injury. We aim to identify prominent disease associations leading to an enhanced understanding of disease progression in young and old mTBI subjects. Our network analysis of comorbidities post mTBI has yielded interesting associations between disease comorbidities in young and old cohorts that could eventually contribute to effective disease management and prevention.

Metrics for capturing vital comorbidities in a disease network

Prevalence is an important metric that identifies vital comorbidities in a population and is widely quantified in numerous epidemiological studies [8, 10]. Our previous study [8] computed the prevalence of various comorbidities after mTBIs. Metric(s) constructed based on graph networks could offer valuable information regarding the presence of comorbidities that play an essential role in disease transitions. Such metrics could also exhibit decreased correlation with prevalence, highlighting the additional information they provide regarding all comorbidities in the population. As mentioned in the results section, betweenness centrality (Fig. 3) exhibits a low correlation with prevalence. For example, BPD and emphysema exhibit low prevalence [8] after mTBIs but are characterized by high values of betweenness centrality (Fig. 3). On the other hand, CP and anxiety are highly prevalent after mTBI [8] but exhibit low values

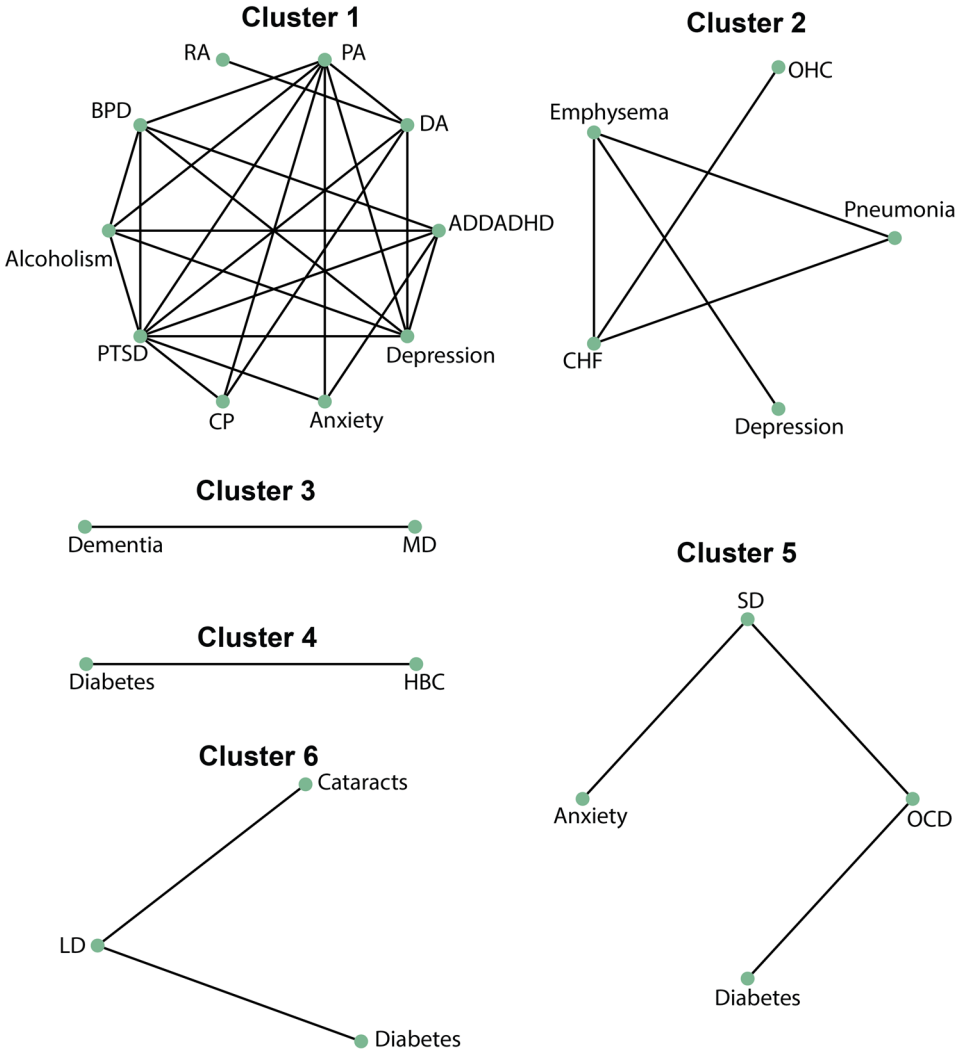

Fig. 6 Application of betweenness centrality-based clustering to the comorbidity network of old mTBI subjects. Individual clusters encompass nodes and edges that represent the comorbidity and the association between them, respectively

of betweenness centrality (Fig. 3). This could mean that despite exhibiting a low prevalence rate, a specific comorbidity could play a vital role in controlling disease transitions by being associated either directly or indirectly with other comorbidities in the network.

Comorbidity associations and shared biological and lifestyle factors mediating the relationship

Our results indicate that psychiatric comorbidities tend to co-occur after mTBI incident(s) (Figs. 4 and 6, and 8), in line with the fact that such illnesses occur at a higher rate in TBI subjects compared to the general public [6–8, 11]. Our study also suggests that OCD is significantly associated with RA in young subjects (Fig. 8). While OCD is a psychiatric condition [43], RA is considered to be a rheumatological and an autoimmune condition [8, 10]. Endorsing our observations, previous literature suggests that OCD may encompass an inflammatory origin [43, 44]. In a nationwide study of Swedish individuals [44], OCD was associated with numerous autoimmune conditions. Although individuals in this study exhibited increased odds of acquiring RA after OCD, the differences were not statistically significant [44]. Additionally, OCD is known to be associated with elevated levels of inflammatory markers such as interleukin [45] and TNF-α [46]. Therefore, our results are indicative of other studies in the literature that inflammation may contribute significantly to the pathogenesis of OCD [43]. OCD was also associated with ADDADHD (Fig. 8), and reports suggest that both conditions exhibit a high degree of association and might involve abnormalities in similar brain networks [47].

One other association worth mentioning is the link between BPD and cardiovascular diseases (CHF, MI, HBC). BPD in the study exhibited comorbidity with cardiovascular conditions (Fig. 4) and more so in young

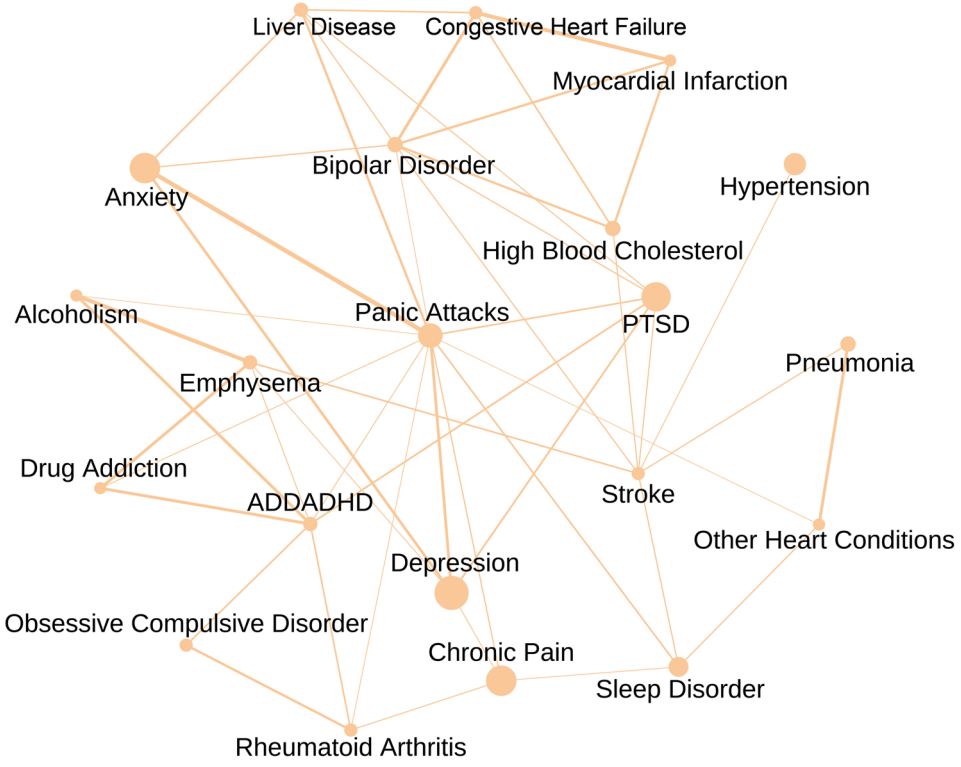

Fig. 7 Disease comorbidity network of young mTBI subjects at 5 years post injury. The nodes in the network represent the comorbidities, while the edges represent associations in the form of phi-correlation coefficient. Node size indicates prevalence, and edge thickness represents the strength of the association

subjects (Fig. 8). Previous results in the field have corroborated our findings [48, 49]. In a recent study that quantified long-term cardiovascular disease risk in patients at a primary care centre, subjects with BPD (severe mental illness) exhibited an increased risk [49]. Similar results were also observed in a prospective cohort study involving Korean subjects [48] where young subjects with BPD exhibited an elevated risk for MI. Although poor lifestyle behaviours (BMI, smoking) are postulated as a possible link between BPD and cardiovascular disease risk [49], such a relationship was not observed in the study of the Korean nationwide cohort [48]. Lastly, BPD in young adults could lead to the early development of certain cardiovascular conditions according to the scientific statement from American Heart Association [50].

The co-occurrence of emphysema with psychiatric conditions is another notable observation (Figs. 4 and 6, and 8). In the study, emphysema was associated with depression in both young and old subjects with mTBI history (Figs. 4 and 6, and 8). Prior literature suggests psychiatric comorbidities (anxiety and depression) are common in subjects with chronic obstructive pulmonary disease (COPD) [51]. Possible risk factors for developing psychiatric conditions after COPD include loneliness due to illness severity, dyspnoea and poor physical health [51]. COPD subjects with psychiatric conditions are also known to exhibit poor prognosis [51].

Similar to other reports in the literature [52], we observed that pneumonia is comorbid with COPD (old subjects) (Figs. 4 and 6). Subjects with COPD are at an increased risk of developing pneumonia due to a variety of reasons, including bronchitis, excessive mucus accumulation to name a few [52]. CHF also tends to co-occur with pneumonia in our study (Figs. 4 and 6), similar to a previous study [53], which reported that patients with CHF exhibit an increased risk of developing a multitude of comorbidities, including pneumonia, which worsens with age.

We also observed an increased predisposition of psychiatric comorbidities with LD in our study. Among the psychiatric comorbidities, anxiety and PTSD were associated with LD, an observation seen only in young mTBI subjects (Figs. 4 and 8). Individuals with LD exhibit an increased risk of developing psychiatric conditions and mood disorders, and possible risk factors include tiredness and changes in recreational lifestyle post-diagnosis [54, 55]. Interestingly, PTSD in the veteran population is accompanied by the occurrence of liver cirrhosis, and those veterans with both conditions exhibit dysbiosis of the gut microbiota compared to those without PTSD, indicating the role of the gut-brain axis on the association

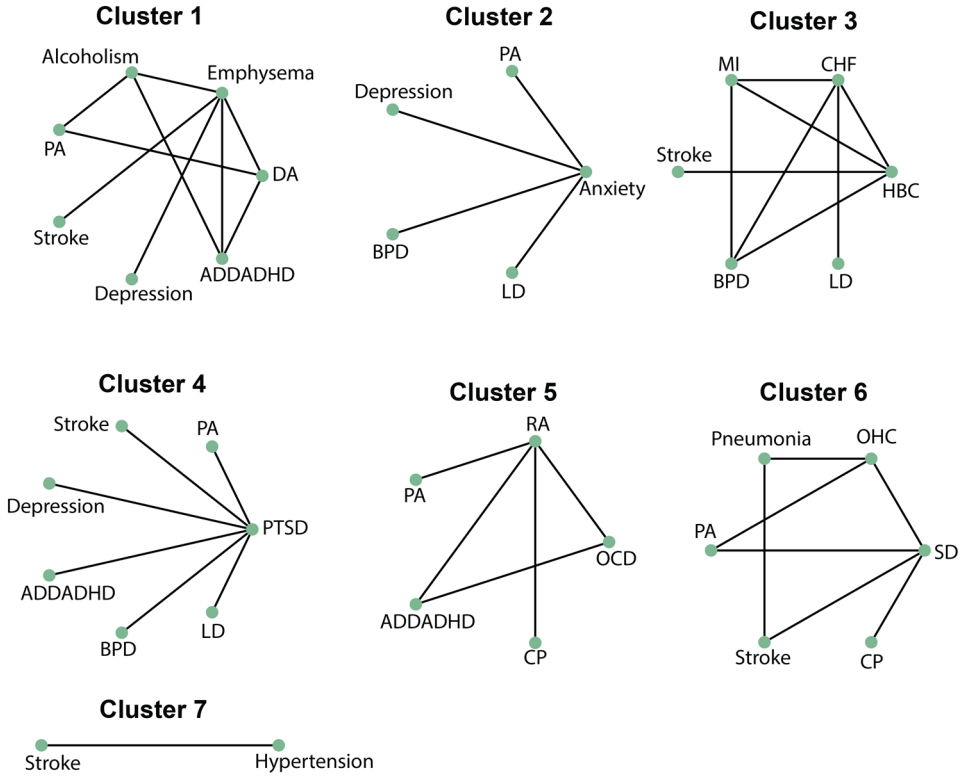

Fig. 8 Application of betweenness centrality-based clustering to the comorbidity network of young mTBI subjects. Individual clusters encompass nodes and edges that represent the comorbidity and the association between them, respectively

[56]. Also, liver problems are one of the reasons for increased mortality among veterans with PTSD [57].

Our study has also highlighted potential links between diseases that typically tend to occur in the elderly population. One such example is the link between LD and cataracts in old subjects (Figs. 4 and 6), also documented in a recent survey involving subjects from the UK biobank [58]. It is assumed that the metabolic modifications caused by the liver condition could eventually lead to the genesis of cataracts [58]. Another comorbidity association that occurs as people age is the connection between MD and dementia (Figs. 4 and 6) [59]. Finally, our study reinforced recent results in the field that cholesterol could be a risk factor for the pathogenesis of OA (Fig. 4) [60], a commonly observed rheumatological condition indicating that OA could exhibit a metabolic origin [61].

Implications for clinical research and practice

Our study results have profound implications for clinical practice and research, especially concerning treating and managing comorbidities after mild brain trauma. First, the associations reported in the study could lead to the development of early intervention plans for subjects affected by the condition. For example, we observed strong associations between BPD and cardiovascular conditions in young subjects. Such observations could motivate early monitoring (screening and health checks) of cardiovascular conditions in subjects with BPD and improve health outcomes in young adults. Additionally, timely administration of preventive medications and drugs (anti-hypertensive drugs) could lower the burden of cardiovascular diseases in subjects with BPD. Further, since one comorbidity could worsen the progression of the other and potentially lead to acquiring other pathologies, intervention programs could be designed to reduce mortality, restore functionality, and improve overall patient outcomes. For example, in subjects with PTSD and liver disease [56], intervention programs could aim to reduce mortality and restore gut-brain functionality in these individuals.

Concerning the treatment of comorbidities, conventional drug therapies to manage a particular comorbidity could affect the pathogenesis of the other and may lead to worsening symptoms. For example, some psychotropic medications may lead to cardiac abnormalities [62]. Hence, in subjects with BPD, the treatment plan should be holistic, taking into consideration the overall medical profile of the subjects, especially given the increased association of the condition with cardiovascular diseases. Additionally, awareness should be raised among the subjects and their families about the possible association between the two conditions (BPD and cardiovascular

Table 1 Difference in comorbidity patterns between young and old mTBI subjects

No.	Description	All subjects	Old subjects	Young subjects
Psychiatric group				
1	Co-occurrence of psychiatric comorbidities	Yes (Clusters 1,3)	Yes (Cluster 1)	Yes (Clusters 1,2,4,5)
2	RA and Psychiatric comorbidities	Yes (Clusters 1,3)	Yes (Cluster 1)	Yes (Cluster 5)
3	CP and Psychiatric comorbidities	Yes (Cluster 1)	Yes (Cluster 1)	No
4	LD and Psychiatric comorbidities	Yes (Cluster 1)	No	Yes (Clusters 2,4)
5	Emphysema and Psychiatric comorbidities	Yes (Cluster 1)	Yes (Cluster 2)	Yes (Cluster 1)
OCD group				
6	Co-occurrence of OCD with RA and ADDADHD	Yes (Cluster 3)	No	Yes (Cluster 5)
Cardiovascular group				
7	Co-occurrence of cardiovascular comorbidities	Yes (Clusters 4, 5)	Yes (Cluster 2)	Yes (Clusters 3,7)
8	Co-occurrence of cardiovascular and pulmonary comorbidities	Yes (Cluster 4)	Yes (Cluster 2)	Yes (Clusters 1,6)
9	Co-occurrence of cardiovascular comorbidities and BPD	Yes (Cluster 4)	No	Yes (Cluster 3)
10	Co-occurrence of cardiovascular and neurologic comorbidities	Yes (Cluster 5)	No	Yes (Cluster 6)
11	Co-occurrence of cardiovascular and rheumatologic comorbidities	Yes (Clusters 5, 6)	No	No
12	Co-occurrence of cardiovascular comorbidities and diabetes	Yes (Cluster 2)	Yes (cluster 4)	No
13	Co-occurrence of cardiovascular comorbidities and cataracts	Yes (Cluster 2)	No	No
Pulmonary group				
14	Co-occurrence of pulmonary comorbidities	Yes (Cluster 4)	Yes (Cluster 2)	No
Neurologic group				
15	Co-occurrence of neurologic comorbidities	Yes (Cluster 5)	Yes (Cluster 3)	No

diseases), which could lead to changes in lifestyle and increased compliance with the treatment plan. Further, accessibility to health infrastructure (physical and mental health) and availability of support systems could lead to meaningful benefits in subjects affected by both conditions.

More research is required to probe the shared pathophysiological mechanisms and pathways behind the association of comorbidities observed in the study. Research in this direction could highlight the shared biological pathways responsible for the association of BPD and cardiovascular conditions, which in turn could lead to the development of targeted drug regimens to treat the condition. Lastly, future research could produce a clearer picture of the role of the immune system [63, 64], mitochondrial dysfunction [65], and the gut-brain axis [56] in the association between PTSD and liver disease.

Limitations of the study and future work

One of the potential drawbacks of the study is the inability to establish directionality when assessing associations between comorbidities. For example, if there is an association between comorbidities A and B in the study, one won't be able to establish if A preceded B or B preceded A. Currently, it may not be possible to construct a directed disease comorbidity network using the data in the database. All that one can say is the presence or absence of a link between the two comorbidities under study. However, constructing directed disease comorbidity networks would be challenging as it requires tedious documentation of each patient visit and the comorbidities diagnosed during the visit [27, 42]. Another limitation of the study is its limited sample size. The number of mild TBI subjects in the TBIMS database [28] those who answered the NHANES survey at 5 years post-injury is 223–228, and we included all of them according to the inclusion criteria discussed in the METHODS section. The sample size could be even lower when considering patient subgroups (old vs. young, male vs. female). Possible reasons could be that mild TBIs may not produce any discernible symptoms, and hence, subjects may not seek medical care leading to underreporting of the actual number of incidents [66]. Additionally, subjects in the database underwent in-patient hospitalization in one of their centers [28]. Additional data could be sought from many other small or outpatient centers, but data integration and subject follow-up could pose significant challenges in obtaining a larger sample size. One of our future aims is to integrate data from different trauma centers and hospitals in the country (India) and develop a large-scale database of TBI subjects along with their follow-up information. Such a database could overcome the limitations of the small sample size observed in the study.

Due to the absence of a control group, enough care should be taken while interpreting the results of associations between comorbidities in the study. While the presence of a control group could have highlighted the unique effects of acquiring mild TBIs, we aim to document the novel patterns and associations between comorbidities in mild TBI subjects, irrespective of whether they were caused by the injury. Our aim is not to quantify the extra burden posed by the comorbidities on the subjects affected by the condition but to draw a clear picture of associations and trends among the 26 comorbidities of interest. Our reasoning is based on the fact that comorbidities and their associations may influence patient

outcomes regardless of whether or not they are caused by the primary impact. It's possible that the comorbidity patterns observed in the study could also be noticed in subjects without a history of TBIs or in TBI subjects before acquiring the index injury. For example, one finding in our study is the association between diabetes and cataracts (Fig. 4) and LD with cataracts, both of which could be noticed in subjects without TBIs [58, 67]. However, it should be noted that certain drugs [68] that are used in the clinical management of TBIs could lead to the early development of cataracts [69]. Additionally, TBIs themselves could accelerate the development of specific comorbidities that occur commonly in healthy subjects [70, 71]. The expedited development of comorbidities could be due to accelerated brain aging where the brains of subjects affected with TBIs undergo gradual atrophy and may appear older than the chronological age of the subjects [72]. This, in turn, could lead to an increased risk of developing numerous medical, psychiatric, and age-related conditions [11, 72]. Therefore, comparing the disease comorbidity network of TBI subjects with a control group could be complicated due to accelerated brain aging and may underestimate the actual disease burden in the TBI population. Carefully curated longitudinal studies that monitor changes in health patterns over time in TBI subjects could aid in understanding the distinct health trajectories in these subjects..

Lastly, the sample of subjects in the study could be heterogeneous owing to sociodemographic factors, age, employment, and injury-related factors. TBI itself is heterogeneous [2, 26], and heterogeneity is considered one of the factors responsible for the poor therapeutic outcome of its candidate drugs [25]. However, we addressed this issue by performing a network analysis of subjects stratified by age (old vs. young subjects). In the future, we plan to extend the study by performing comorbidity network analysis for subjects based on sex and different TBI pathoanatomic types to combat heterogeneity, as recommended in a study [25]. Lastly, the presence of ascertainment bias cannot be ruled out, as comorbidities explored in the study could have exhibited a persistent time course and gone unnoticed before the incidence of mTBI [8].

Conclusions

Our study demonstrates the effectiveness of translating disease prevalence data into a graph-theoretical framework. This approach yielded insights into comorbidity patterns following mTBIs, aligning with previous research [34, 44, 50, 56], and presents a highly adaptable methodology. The power lies in representing any measurable population characteristic as nodes in a network, with edges signifying associations between them. This not only deepens our understanding but leverages existing data efficiently. Since TBI subjects experience a plethora of comorbidities over time [10, 11, 27], the study results can be effectively employed for monitoring comorbidities and establishing effective preventive care. Additionally, the approach could be utilized for machine learning-based identification of high-risk patient cohorts [27].

Abbreviations

HBC	High Blood Cholesterol
LD	Liver Disease
PA	Panic Attacks
BPD	Bipolar Disorder
ADDADHD	Attention Deficit Disorder/Attention Deficit Hyperactivity Disorder
MI	Myocardial Infarction
CHF	Congestive Heart Failure
OCD	Obsessive-Compulsive Disorder
OA	Osteoarthritis
RA	Rheumatoid Arthritis
OHC	Other Heart Conditions
CP	Chronic Pain
SD	Sleep Disorder
MD	Movement Disorder
PTSD	Post-Traumatic Stress Disorder
DA	Drug Addiction
TBIs	Traumatic Brain Injuries
mTBIs	Mild Traumatic Brain Injuries
NHANES	National Health and Nutritional Examination Survey

Supplementary Information

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Supplementary Material 1: Fig. S1: Phi-correlation coefficient matrix of different comorbidity pairs for all mTBI subjects. Fig. S2: Illustration of degree centrality in graph networks. Fig. S3: Illustration of betweenness centrality in graph networks. Fig. S4: Illustration of eigenvector centrality in graph networks. Fig. S5: Illustration of the implementation of betweenness centrality clustering algorithm. Table S1: List of removed nodes applying the betweenness centrality clustering algorithm to the comorbidity networks of all young and old mTBI subjects. Supplementary methods: Overview of the construction of the disease comorbidity network, mathematical description of the centrality measures, and betweenness centrality clustering algorithm.

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Author contributions

Kaustav Mehta: Methodology, Software, Validation, Formal Analysis, Data Curation, Visualization, Writing - Review and Editing Shyam Kumar Sudhakar: Conceptualization, Methodology, Software, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing - Original Draft, Writing - Review and Editing, Visualization, Supervision, Project Management, Funding Acquisition.

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Data availability
All programming scripts used in the analysis and the secondary data that resulted out of the study will be available on reasonable request.

Declarations

Ethics approval and consent to participate
The study involves secondary analysis of data of de-identified subjects and hence the need for ethics approval was waived by the institutional review board of Krea University. Informed consent is not applicable since this study involves secondary analysis of data from a database.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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