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Comorbidity Networks in Cardiovascular Diseases: Recreating the results of a study and the Analysis of DC-SBM vs Infomap Community Detection vs Louvain Community Detection

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Comorbidity Networks in Cardiovascular Diseases: Recreating the results of a study and the Analysis of DC-SBM vs Infomap Community Detection vs Louvain Community Detection

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I. Introduction

Cardiovascular diseases are one of the leading causes of death globally, and often develop into systemic failure due to “multiple connections to organismal metabolism,” leading them to be associated with comorbidities or multimorbidities. As cardiovascular diseases are often very complex, Cardiovascular Comorbidity Networks, or CVC Networks, have been playing an increasingly important role in “elucidating the higher-order interactions underlying traits such as atherosclerosis, cardiac hypertrophy, heart failure, and arrhythmias,” giving scientists and medical professionals a higher understanding in the treatment of these complex diseases.¹

A 2020 study published in the *Frontiers in Physiology* created a comorbidity network using cases from the National Reference Hospital for Cardiovascular Diseases in Mexico City and examined the patterns of comorbidity and genetic interactions in order to determine if it would aid in the understanding and management of cardiovascular diseases.² Our

objective is to recreate the results of the study using the same methods of network and clustering analysis—the study performed a clustering analysis using an Infomap Community Detection implementation—as well as run our own Louvain Community Detection, and DC-SBM clustering analysis and compare the results to that of the Infomap implementation.

The network provided is an undirected single component connected network in which the nodes represent the disease code (corresponding to the disease name in ClinVar DB), and the edges represent the pairing or coexistence of the two diseases. The data is taken from a large set of cases diagnosed with cardiovascular conditions at the national reference hospital for cardiovascular diseases in Mexico.

The terms “cluster,” “partition,” “module,” “group,” and “community” will all be used interchangeably throughout this paper to represent the subdivisions of nodes created in our community detection analysis.

II. Materials and Methods

II.1 Data Information

Our data comes from the paper we are attempting to recreate. We use the “ComNet_all.csv” file to load the network data into the different community detection models that we use. This CSV data file was created by the researchers from the paper using real cardiovascular condition diagnoses and the

¹ Lusis Aldons J,m Weiss Hames N., *Cardiovascular Networks: Systems-Based Approaches to Cardiovascular Disease, Circulation*. 2010;121:157–170
<https://doi.org/10.1161/CIRCULATIONAHA.108.847699>

² Cruz-Ávila Héctor A., Vallejo Maite, Martínez-García Mireya, Hernández-Lemus Enrique *Comorbidity Networks in Cardiovascular Diseases* Frontiers in Physiology Vol. 11, 2020
<https://www.frontiersin.org/article/10.3389/fphys.2020.01009>

ClinVar Database. Once we load this data into a normal, undirected NetworkX graph, we will perform the same network statistics used in the paper we are trying to recreate.

II.2 Cardiovascular Comorbidity Network Analysis (CVC network)

We will be using the ComNet_all.csv file to load network data onto an undirected NetworkX network. In this network, the nodes are represented by ICD-10 code of the diagnosis, and links between nodes correspond to the coexistence of two diagnoses.

To perform network statistics we will be using the built-in NetworkX functionality, and outputting the results to a CSV file (for comparison to the results of the actual paper).

II.3 Cardiovascular Comorbidity Network Modularity Analysis

To perform modular analysis on the CVC network, we will be using three models: Infomap, DC-SBM, and Louvain Method. For each of these models, the modular analysis will be very similar to each other, and to the analysis performed in the paper. The goal of the paper was to unveil comorbidity patterns via cluster analysis such that we are able to see clusters of different diseases that are more commonly related to each other.³

The general process for the modular analysis using the three different models is fairly straightforward. Firstly, using each of the models we will obtain the best partition we can. From this partition we will create a modular representation of the CVC network. Each module from the partition will be labeled by a single ICD-10 disease code. This disease code is the result of computing the page-rank index (PRI) of every node in each module from the partition, and then labeling the module with the ICD-10 disease code of the node in the module with the largest PRI value. Now for each module

in the original partition, we run the model again to find the partition to create submodules. We label the submodules of the new module partitions the same way as the named the top modules. After we have the modules and submodules returned from each model, we will create graphical visualizations of them and convert the ICD-10 disease codes of each module/submodule into its corresponding disease/diagnosis. From these translations of the disease codes, we can finally draw conclusions in regards to the comorbidity structures in the CVC network.

II.3.A Infomap Model Details

The InfoMap Model was used by the researchers of the article we are trying to recreate, Cruz-Ávila, Vallejo, Martínez-García, and Hernández-Lemus, to visualize and create these “CVCModules.” InfoMap Model is a community detection algorithm based on the map equation. Map equation utilizes the idea that networks carry flow, and this flow is dependent on the edges of a network which induce movement across a network: “Tells us how efficient the optimal code would be for any given partition, without actually devising that code. That is, it tells us the theoretical limit of how concisely we can specify a network path using a given partition.”⁴ The methodology used in the paper to create these modules initially ran InfoMap model on the undirected comorbidity network.

In our attempt to reproduce the results of the paper on CVC modules, we discovered our results to vary massively from what was expected. Our implementation of the InfoMap Model utilized the InfoMap package available on PyPi, which was Doctor Rosvald’s implementation of the model.

³ Cruz-Ávila, et. al, 2020

⁴ Rosvall, M., Axelsson, D. & Bergstrom, C. The map equation. *Eur. Phys. J. Spec. Top.* 178, 13–23 (2009). <https://doi.org/10.1140/epjst/e2010-01179-1>

After several iterations of trying to resolve this issue, we resorted to trying to use a solution landscape to see all possible alternate solutions, other than the solution partition returned by the Infomap model.

A solution landscape is a very helpful tool in analyzing modularity within a network. In our research, we used the solution landscape to first see how many runs of Infomap Model we would need to attain a solution with a predefined distance threshold and accuracy at level 0.90.

II.3.B Louvain Community Detection Details

The Louvain method is a modularity maximization approach for community detection. This model will recurse over nodes and keep merging modules on a single node, which is what we want to see in our experiments. Our implementation of this required the installation of the community api (known as python-louvain package) from PyPi.

The resolution parameter of the Louvain algorithm defines the threshold to which the algorithm will favor either larger or smaller communities. If the resolution is set to value less than one, then the algorithm will favor larger communities, and vice versa. Therefore in our simulation to produce the real best partition, we created a hundred louvain partitions on the original network, whose resolutions ranged from 0.1 to 10, stepping by 0.1 for each resolution. For each partition a modularity score was computed, and only the partition with the maximum modularity score was returned from the simulation.

From the resulting best simulated partition, we carry on with the general process described in **II.3** and perform modular analysis and submodular analysis.

II.3.C DC-SBM Details

In addition to Louvain and Infomap clustering / community detection, we wanted to see if DC-SBM partitioning would yield

different results than those of the study. DC-SBM (Degree-Corrected Stochastic Block Model) is a “modular generalization of a random graph with specified degree structure.”⁵ As our model is an undirected multigraph network, we can use DC-SBM analysis to find a relatively realistic representation of our network’s structure.

In order to implement the DC-SBM clustering, we first attempted to use a greedy heuristic function written in Python (that had previously been used for problem set 6 in this course), but due to the large amount of nodes and edges in our dataset, we concluded this approach was inefficient and would take too much time to run. Instead, we used the `DCSBM.estimate` function from the `randnet` package in R to generate the partitions (as seen in file `DCSBM.R`), and then exported the partitions back into Jupyter for further analysis (`DCSBMCommunityDetection.ipynb`).

For the initial partitioning of the entire network, we chose to create 5 partitions as was done previously in the Infomap and Louvain Community Detection. After each partition was found, the “parent node” of each module was chosen based on the highest page ranked node in each module (which is also equivalent to the node with the highest degree or the most connections in the module).

Each module was then partitioned once more into additional submodules, with the amount of partitions varying based on both what was done in our previous methods of community detection and based on the partitioning done in the study, which noted that each cluster “included between two and eight different comorbidity sub-clusters.”⁶ This partitioning was done by first removing the parent node from each module (so the parent node would not then again be the parent node of one of its

⁵Clauset, Aaron “Modular Networks Structure”, CSCI 3352 Lecture Notes 5

⁶Cruz-Ávila et. al, 2020

submodules), creating a subgraph, and then generating an edge list that was then imported into R for the DCSBM partitioning. Something to note is that when creating the edge list, there were some nodes in Cluster 1 and Cluster 3 that were not connected to any other nodes which resulted in a smaller network than the original cluster (i.e. Cluster 1 originally had 335 nodes but the edgelist only contained 129 of those nodes). Although this means some nodes were lost in the partitioning, we felt that since we were only focusing on the nodes with the highest degrees, the nodes that were lost (due to having a degree of 0) were not as relevant to our analysis.

These partitions were then analyzed in the same way as the previous modules, as described in section II.3.

III. Results

III.1 Cardiovascular Comorbidity Network

Recreation Results

Our first goal was to recreate the network node analysis that was done in the study. We calculated the clustering coefficient, eccentricity, degree, betweenness centrality and closeness centrality of each node in the network and stored it all in “recreated_data.csv” found in the GitHub repository for this project. Table 1 in Section VI contains a sample of some of that node data. We used the native NetworkX functions to find each of these values.

III.2 CVC Infomap Modular Analysis Results

As mentioned in the Materials and Methods section, the Infomap implementation of the CVC network did not go according to plan. The results of the process will be discussed below.

To create our partition, we first loaded the comorbidity network data csv into a normal, undirected networkx graph. We then created an instance of InfoMap, added the networkx graph

to the instance of Infomap, and ran the model (printing out all the top modules and all the nodes with their respective modules). The output of this model was completely unexpected: there were 11 top modules, with 1421 nodes in module one, out of a total of 1474 nodes in the network. These results did not seem to make any sense since we know that in the paper the comorbidity network was broken down into evenly sized modules. After several iterations of trying to resolve this issue, we resorted to trying to use a solution landscape to see all possible alternate solutions, other than the solution partition returned by the Infomap model.

For the solution landscape, we had defined our accuracy level to be 0.90 and the distance threshold to be 0.002. After continuously producing new Infomap solution partitions to meet the solution landscape requirements, the outcome was that our solution landscape contained 31 clusters and 150 partitions, where 100% of the partitions fit in the partition clusters from the 150 training clusters. The data, which was taken with bootstrapped 95% confidence intervals, from this was then plotted where the number of partitions versus the validation score was used to visualize to see the most optimal solution.

We then chose to only include the 20 best clusters and 126 of the partitions. From these clusters and partitions, we computed the pairwise cluster center distances. The cluster center distances were placed into a partition distance matrix which is then converted to two-dimensional coordinates using the UMAP library, and finally visualized in a contour plot. Pictured below is the partition distance matrix of the solution landscape, as well as a contour plot of the solution landscape.

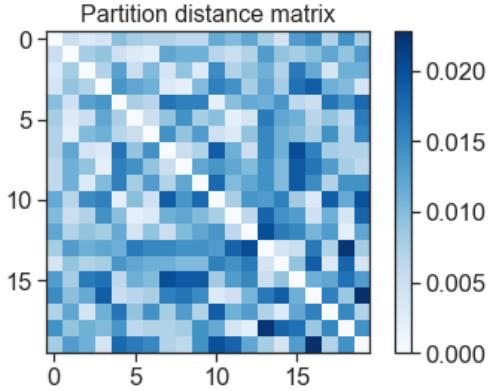


Figure 1: Partition distance matrix of pairwise cluster distances for solution landscape

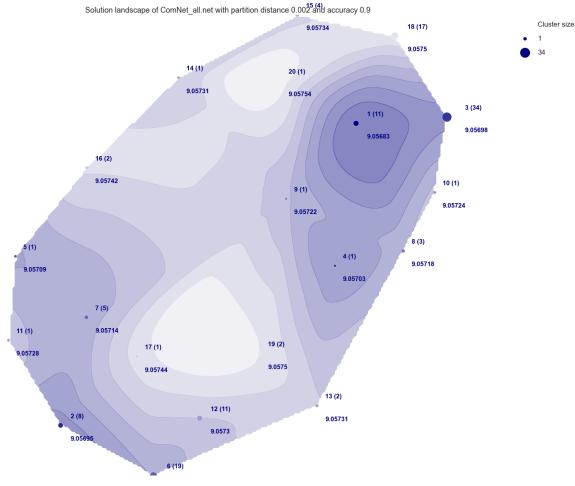


Figure 2: Contour plot of the solution landscape

In our contour plot we can see that module one which has 11 partitions was the best result in our solution landscape. Moreover, module two with 8 partitions was our second-best result. The problem we run into here is that once that module one solution is taken and implemented to the comorbidity undirected network graph, we still get the same solution as we did before using a solution landscape. The visualization of the module one solution showed groups of nodes connecting to other groups of nodes, which is not the modularity we are trying to achieve. This led us to move on from an Infomap modular analysis to attempt the Louvain community detection analysis.

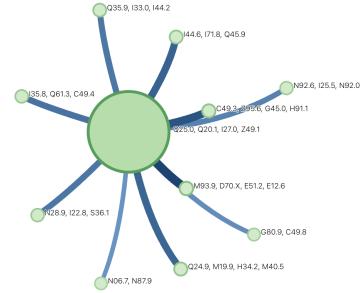


Figure 3: Modular View of Infomap module solution 1

III.3 CVC Louvain Community Detection Results

The experiment on the comorbidity network data began with running the community api “best_partition method” on the network data. The result of the best partition was 6 modules, with an overall modularity of 0.26512. We wanted to iterate on our model to find the actual best partition by modifying the resolution parameter of the Louvain community detection algorithm.

After running the resolution simulation (described in II) to produce the best partition, we found that when the resolution was set to 0.9, we were able to maximize the modularity score. Furthermore, we visualized the range of resolution values versus the modularity score, to validate our results.

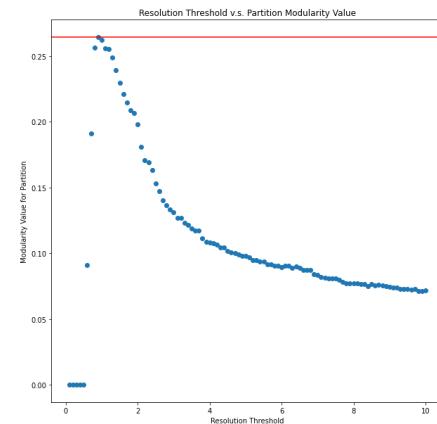


Figure 4: Graph of partition resolution v.s. The partition modularity score

The best partition from our simulation resulted in a total of 5 modules with a

modularity score of 0.2644. In each of the 5 modules, we found the node with the highest page-rank value to represent the entirety of the module. However, it should be noted that for module two, we used the node with the second largest page-ranked value to represent the whole module. Initially, we found that the node with ICD-10 code Z01.7 had the highest page-ranked value. The ICD-10 code translation for Z01.7 translates to “Laboratory examination,” which was a very vague description to represent the whole module. Moreover, this description did not represent the other nodes in the module accurately, and therefore we chose the node with ICD-10 code N18.9 to represent module two.

To follow up on analysis of the modules that resulted from our simulated best louvain partition, we performed subcluster analysis on each module. In the sub cluster analysis, we find the louvain communities in each module, and perform the same visualizations as we did previously for the entire comorbidity network modules. We found that module zero had 4 subclusters, module one had 14 subclusters, module two had 6 subclusters, and module three had 7 subclusters. We did not run subcluster analysis on module four since it contained a total of 4 nodes and louvain communities would not run on this number of nodes.

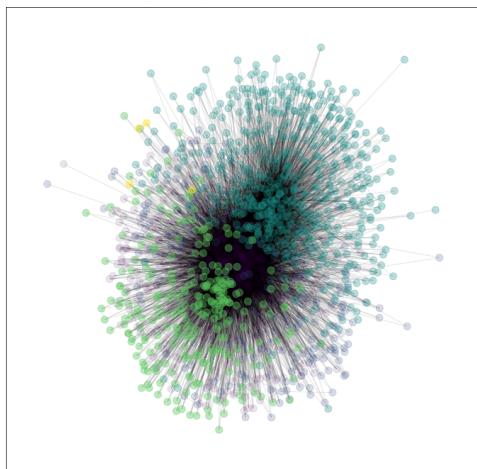


Figure 5: Cardiovascular comorbidity network displayed and highlighted communities via the result of the Louvain Community partition. Mainly shows the number of nodes in each cluster and the top node with its ICD-10 translation

III.4 CVC DC-SBM Results

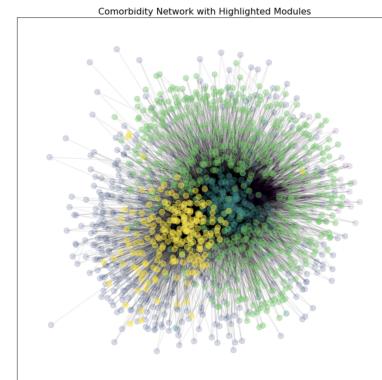


Figure 6: Model of the five communities found using DC-SBM, highlighted in the CVC Network.

The three communities that were selected for analysis in the study were “Other forms of chronic ischemic heart disease (I25.8); Chronic kidney disease, unspecified (N18.9) and Other specified congenital malformations of heart (Q24.8).” Of the five communities found in the DC-SBM analysis, two of the communities had the same parent node as those selected by the study, Cluster 0 with Q24.8 and Cluster 4 with N18.9. I25.8 was the parent of the largest submodule in Cluster 2 (Z01.7), which represents general laboratory examination. Tables 4 - 9 contain the data found for each of these modules and their submodules.

IV. Discussion

IV.1 CVC Infomap Community Detection Discussion

As we saw from the results of the Infomap Model, as well as the Infomap solution landscape, the implementation was not a

success, and so we were unable to recreate the results of the study in which they used Infomap. However, we compensated for this by running the Louvain community detection model instead.

After several attempts to try resolve this modularity issue we face when running Infomap Model on the network data, we came to the conclusion that the Infomap implementation described in the paper we are trying to recreate, does not fully describe the process of transferring the data from the comorbidity network into the Infomap model. There must have been some sort of data manipulation/grooming that occurred before the undirected comorbidity network data was implemented into Infomap. Since the paper does not provide this detail, we thought it would be best to move on from Infomap, and use another community detection algorithm.

IV.2 CVC Louvain Community Detection Discussion

Looking at the results returned from the Louvain community detection implementation, we can see that we created a pretty accurate, and modular representation of the CVC network.

In the implementation of Infomap and the clusters that resulted from the paper, the researchers chose to pick the 3 largest modules and identify the top node based on the page-ranked index value. The paper identifies these 3 nodes to represent the 3 largest modules: Q24.8, I25.8, and N18.9. Looking back at the summary table in table 2, we can see that modules 0, 2, and 3 are the largest modules; whose corresponding nodes are: I25.8, N18.9, and Q24.8. It is very interesting to see that the Louvain Community detection produced the same nodes as the paper, in the 3 largest modules.

Furthermore, it is important to note that everytime the Louvain best partition was run on a top module in this community structure, we got different results every time. However, this

was expected to happen since Louvain is a modularity maximization approach.

Louvain Module Zero and its submodules

Discussion:

We can see in Table 2 that module zero is represented by node I25.8 which corresponds to “Other forms of chronic ischemic heart disease”. Chronic ischemic heart disease is defined as: “encompasses a variety of conditions that result in a mismatch between myocardial oxygen supply and demand.”

Submodule zero in module zero is represented by the node I42.4 which corresponds to “Other hypertrophic cardiomyopathy”. Hypertrophic cardiomyopathy or HCM is a “genetic disorder that is characterized by left ventricular hypertrophy unexplained by secondary causes and a non dilated left ventricle with preserved or increased ejection fraction.”

We can see how I25.8 and I42.4 may be comorbid, since HCM has left ventricular hypertrophy that is due to unknown secondary causes. Purely speculating, but ischemic heart disease could be the secondary cause for HCM.

Submodule one was represented by Z95.5, whose ICD-10 translation is “Presence of coronary angioplasty implant and graft”. This is also a very interesting pair, since the presence of coronary angioplasty refers to “procedure used to open clogged heart arteries.”⁷ There is a possibility that the coronary angioplasty was due to chronic ischemic heart disease. Since a chronic ischemic heart is characterized by a mismatch between the oxygen supply and demand, this could indicate that there is a clog somewhere in the heart. Due to this clog, a coronary angioplasty might be required, which

⁷ Mayo Clinic. (n.d.). *Coronary Angioplasty and Stents*, <https://www.mayoclinic.org/tests-procedures/coronary-angioplasty/about/pac-20384761>

opens the clogs up. Moreover, there is a connection between submodule zero (I42.4) and this submodule one. We can infer that there is a possibility that a coronary angioplasty could be needed for HCM.

Submodule two is represented by Z01.4, which relates to “Encounter for gynecological exam.” This submodule is very puzzling because at first it seems very strange to try to connect gynecological exams with chronic ischemic heart disease. There is a strong possibility that this submodule appeared in top module zero solely based upon chance from the Louvain best_partition method. It could also be the case that during gynecological exams, something in the exam itself raises a concern about the heart, which leads to the diagnosis of chronic ischemic heart disease (this could be a stretch).

Submodule three is represented by M00.8 which corresponds to “Arthritis or polyarthritis due to other bacteria”. This is another submodule that seems to have a confusing connection with chronic ischemic heart disease. However, after further research, we found that “The increase in Rheumatoid arthritis (RA) associated mortality is predominantly due to accelerated coronary artery and cerebrovascular atherosclerosis with increased risk of ischemic heart disease about 50% in RA patients compared to controls.”⁸ This research paper shows us that there is a clear comorbid connection between arthritis and chronic ischemic heart disease, which is a connection that seems extremely uncommon.

⁸ El Bakry SA, Fayed D, Morad CS, Abdel-Salam AM, Abdel-Salam Z, ElKabary RH, El Dakrny AHM. Ischemic heart disease and rheumatoid arthritis: Do inflammatory cytokines have a role? Cytokine. 2017 Aug;96:228-233. doi: 10.1016/j.cyto.2017.04.026. Epub 2017 May 3. PMID: 28477538.

Louvain Module Two and its Submodules

Discussion:

In Table 2, module two is represented by N18.9 which translates to “Chronic kidney disease, unspecified”. There are 554 nodes in this module, making it the largest module in our partition, with a total of six subclusters.

Submodule zero is represented by D35.0, “Benign neoplasm of adrenal gland”. This condition is known as aldosteroma, which is basically a tumor that is not cancerous, however produces elevated levels of aldosterone. This condition can lead to Conn’s syndrome which can result in low levels of potassium, putting individuals with this condition at risk of stroke, heart attack or kidney failure.⁹ Here we can see a clear correlation between this benign neoplasm of the adrenal gland and chronic kidney disease. If a patient who is diagnosed with aldosteroma develops Conn’s syndrome, there is a chance for kidney failure. This kidney failure could develop into a chronic kidney disease.

Submodule one is represented by node Z53.8 which translates to “Procedure or treatment not carried out for other reasons”. This submodule seems to not really have any correlation to chronic kidney disease. The best speculation to this correlation is that there is the possibility that because of chronic kidney disease, a patient could not continue with procedure/treatment for another condition. However, this submodule could largely be the result of some inaccuracy in the louvain best partition.

Looking at submodule two, we see that it is represented by Z49.0, “Preparatory care for renal dialysis.” Renal dialysis is defined as treatment to perform the function of what healthy kidneys would do, since your kidney

⁹ NYU Lang One Health, (n.d.), *Types of Adrenal Tumors*
<https://nyulangone.org/conditions/adrenal-tumors/types>

function has failed. We can see an evident correlation between chronic kidney disease and renal dialysis. There is the possibility that a patient has to go through preparatory care for renal dialysis because of chronic kidney disease. It could be the case that the chronic kidney disease, caused kidney failure, leading to a necessary renal dialysis.¹⁰

In submodule three, the node that represents the submodule is N32.1 which translates to “Vesicointestinal fistula”. Vesicointestinal fistula is defined as “an abnormal communication between the intestine and the bladder.”¹¹ The vesicointestinal fistula usually occurs secondary to diverticular disease already in a patient. There has already been a connection found where patients who have polycystic kidney disease have a predisposition to diverticular disease. An inference we can make on this is that a patient with polycystic kidney disease has a disposition to forming this fistula, since they already have a risk of developing a diverticular disease.¹²

Submodule four was categorized by N13.1, which is “Hydronephrosis with ureteral stricture, not elsewhere classified”. Unpacking this disease translation, ureteral stricture is when the tube of the ureter that carries urine delivers urine from the kidney to the bladder, has narrowed. Due to the now narrow tube, the kidney cannot function as it once did, leading to hydronephrosis where the kidney is dilated.¹³

¹⁰ National Kidney Foundation, (n.d.), *Dialysis* <https://www.kidney.org/atoz/content/dialysisinfo>

¹¹ Shaydakov ME, Pastorino A, Tuma F. Enterovesical Fistula. [Updated 2021 Sep 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK532936/>

¹² Subbiah A, Mahajan S, Yadav RK, Agarwal SK. Colovesical fistula: a rare complication after renal transplantation. *BMJ Case Rep.* 2018;2018:bcr2017222682. Published 2018 Jan 6. doi:10.1136/bcr-2017-222682

¹³ City Of Hope, (n.d.), *Ureteral Strictures Facts* <https://www.cityofhope.org/clinical-program/ureteral-strictures/ureteral-strictures-facts>

This is particularly interesting because, if a patient has hydronephrosis from a urethral stricture, then they could be predisposed with chronic kidney disease. If the kidney is dilated and not functioning properly, this would most likely give a chance for a kidney disease to develop that could, in turn become chronic. This shows that there is a comorbid relationship between these two diseases.

Submodule five is represented by E12.6, which corresponds to “Malnutrition-related diabetes mellitus with other specified complications”. It is evident that these two diseases would be comorbid since we know that diabetes will cause high blood glucose, which affects the kidneys. High blood sugar can damage vessels in the kidneys, which could turn into a chronic kidney disease. You are more likely to develop kidney disease as a result of having a high blood glucose or a high blood pressure. Both of these symptoms are common in diabetic patients, which shows how diabetes and chronic kidney disease could be comorbid.¹⁴

Louvain Module Three and its Submodules Discussion:

Looking at Table 2, we can see that module three is represented by Q24.8, “Other specified congenital malformations of the heart”. Congenital malformation of the heart refers to the problems within the structure of the heart. Congenital malformations of the heart is one of the most common types of birth defects.¹⁵ In this module, we can see that there are 7 subclusters.

For submodule zero, it is defined by node O99.8, “Other specified diseases and conditions complicating pregnancy, childbirth, and puerperium”. This is a strange node to

¹⁴ National Institute of Diabetes and Digestive and Kidney Diseases, (n.d.), *Diabetic Kidney Disease* <https://www.niddk.nih.gov/health-information/diabetes/overview/preventing-problems/diabetic-kidney-disease>

¹⁵ Medline Plus, (n.d.), *Congenital Heart Defects*, <https://medlineplus.gov/congenitalheartdefects.html>

represent the subcluster, however above we noted how congenital malformations of the heart are one of the most common birth defects. Perhaps there can be a connection drawn between the disease/condition that complicates the pregnancy and the congenital malformation of the heart. There is a possibility that the complication of the pregnancy itself results in the heart defect.

Submodule one is represented by F80.1, which was characterized as “Expressive language disorder”. There has not been too much research regarding the correlation between congenital heart malformations and expressive language disorder, however there have studies relating congenital heart disease to speech impairment. It has been noted that “Many children with complex CHD have delays or deficits in linguistic skills.”¹⁶ We could further infer from this that heart disease that leads to congenital malformation of the heart, could affect linguistic skills. Therefore, we could draw a possible conclusion that expressive language disorder is comorbid with congenital malformations of the heart.

In submodule two, we see that the node that represents this submodule is Q96.9, which relates to Turner’s syndrome. Turner’s syndrome is defined as “a condition usually associated with reduced final height, gonadal dysgenesis, and thus insufficient circulating levels of female sex steroids, and infertility.”¹⁷ With Turner’s syndrome, the risk of congenital heart malformations is increased. These malformations include: “bicuspid aortic valves,

¹⁶Sick Kids, (n.d.), *Speech & language of children with heart disease* <https://www.aboutkidshealth.ca/article?contentid=1702&language=english>

¹⁷ Gravholt CH. Turner syndrome and the heart: cardiovascular complications and treatment strategies. Am J Cardiovasc Drugs. 2002;2(6):401-13. doi: 10.2165/00129784-200202060-00005. PMID: 14727955.

aortic coarctation, other valve abnormalities, and septal defect.”¹⁸ Therefore, we can conclude that Turner’s syndrome and congenital heart malformations are in fact comorbid, according to this research paper.

Submodule three is defined by Q25.7, “Other congenital malformations of pulmonary”. Congenital malformations of pulmonary are basically defects in the pulmonary valve. In this condition, the heart is not able to pass blood to the lungs, due to a solid tissue blocking the valve. It is apparent that a congenital malformation of the pulmonary could be comorbid with congenital malformation of the heart. The congenital malformation of the heart encompasses this pulmonary defect.¹⁹

In submodule four, the top node is Z33.X, which correlates to “Pregnant state”. There is not much research to be done on the vague description of “pregnant state”, however we can make inferences based on the other other comorbidities in this module. Since we know that congenital heart malformations are very common birth defects, we could be led to believe that a fetus before being born (in a pregnant state) is predisposed to congenital malformations of the heart. Since there is a possibility that a fetus develops a heart defect, we could say these two are comorbid.

Submodule five is represented by H50.8, “other specified strabismus”. Strabismus is a condition in which an individual has crossed eyes, or just a misalignment of the eyes.²⁰ After conducting some research, we found a study that was trying to describe the ocular findings in patients with congenital heart disease. The conclusion of this study was that “Patients with CHD are at a high risk for ocular pathology and

¹⁸ Ibid

¹⁹ Mayo Clinic, (n.d.), *Pulmonary Atresia* <https://www.mayoclinic.org/diseases-conditions/pulmonary-atresia/symptoms-causes/syc-20350727>

²⁰ Hopkins Medicine, (n.d.), *Strabismus* <https://www.hopkinsmedicine.org/health/conditions-and-diseases/strabismus>

need screening for various ocular abnormalities.”²¹ Therefore, we could be able to draw a conclusion that a heart disease that causes a congenital heart malformation could also increase the risk of contracting strabismus.

Submodule six has the top node P23.6, which translates to “Congenital pneumonia due to other bacterial agents.” According to a research paper on studying the “Mortality and morbidity in patients with congenital heart disease hospitalized for viral pneumonia,” patients with congenital malformations of the heart should be considered high risk individuals, should they contract viral pneumonia.²² Therefore, these diseases do seem to be comorbid, in that, a patient with congenital malformations of the heart could severely be in danger should they have viral pneumonia as well.

IV.3 CVC DC-SBM Community Detection Discussion

As we are using the communities created from the DC-SBM partitioning to compare to the results of the study, we will only be analyzing the three communities that contain the disease codes analyzed in the study (Cluster 0 (Q24.8), Cluster 2 (I25.8), and Cluster 4 (N18.9)).

Analyzing Cluster 0 - Q24.8

Most of the subclusters in Cluster 0, which is represented by “Other specified congenital malformations of heart” (**Q24.8**), represent a more specific malformation of the heart present at birth, which fits into the

²¹ Mansour AM, Bitar FF, Traboulsi EI, Kassak KM, Obeid MY, Megarbane A, Salti HI. Ocular pathology in congenital heart disease. *Eye (Lond)*. 2005 Jan;19(1):29-34. doi: 10.1038/sj.eye.6701408. PMID: 15184955.

²² Diller G, Enders D, Lammers AE, et al. Mortality and morbidity in patients with congenital heart disease hospitalized for viral pneumonia. *Heart* 2021;107:1069-1076.

description of the overall module. The only subcluster that is not represented by a disease that directly has to do with a congenital malformation of the heart is subcluster 2 code I27.0, which represents primary pulmonary hypertension, “a rare lung disorder in which the blood vessels in the lungs narrow and the pressure in the pulmonary artery rises far above normal levels.”²³ According to an article published in the European Respiratory Review in 2012, however, “Pulmonary arterial hypertension (PAH) is a frequent complication of congenital heart disease (CHD),” which is supported by the comorbidities in Cluster 0.²⁴

The subcommunities found in Cluster 0 were different from those analyzed in the study. As shown in Table 10, the comorbidities analyzed had more to do with lung failure. The comorbidities chosen in the study were found using Jaccard Index, meanwhile we utilized the degree of the node, so this could be why we found different results.

Analyzing Cluster 2 - Z01.7 (containing I25.8)

Cluster 2, which is represented by “Laboratory Examination” Z01.7, has a very general description of the parent node which could mean that the resultant subclusters are also very general. However, the four subclusters all seem to be represented by diseases that have to do with narrowed arteries and the complications that come with that. Subclusters 1 and 3 represent the chronic or acute forms of ischaemic heart disease (respectively), a “term given to heart problems caused by narrowed

²³ John Hopkins Medicine, Primary Pulmonary Hypertension <https://www.hopkinsmedicine.org/health/conditions-and-diseases/primary-pulmonary-hypertension>

²⁴ Pulmonary arterial hypertension associated with congenital heart disease Michele D'Alto, Vaikom S. Mahadevan European Respiratory Review Dec 2012, 21 (126) 328-337; DOI: 10.1183/09059180.00004712 <https://err.ersjournals.com/content/21/126/328>

heart (coronary) arteries that supply blood to the heart muscle.”²⁵ Ischaemic heart disease is also often characterized to be caused by plaque build up in the arteries, also known as atherosclerosis, which represents subcluster 2.²⁶ Additionally, atrial fibrillation and flutter, which represents subcluster 0, is associated with increased risk of death in patients with ischaemic heart disease.²⁷ The comorbidities in Cluster 2 support the findings of this increased risk.

Analyzing Cluster 4 - N18.9

Cluster 4, represented by N18.9 “Chronic kidney disease, unspecified”, contains subclusters that are all represented by kidney related complications or procedures. “Hyperuricemia without signs of inflammatory arthritis and tophaceous disease” (**E79.0**), which represents subcluster 4, has been associated with an increased risk in kidney damage.²⁸ Z96.0, “Presence of urogenital implants,” is the ICD-10 code used to indicate the presence of a kidney stent. Z49.1 and Z49.2 are both codes for the fitting and adjustment of different types of dialysis catheters, which is often used as a

²⁵ Institute of Medicine (US) Committee on Social Security Cardiovascular Disability Criteria. Cardiovascular Disability: Updating the Social Security Listings. Washington (DC): National Academies Press (US); 2010. 7, Ischemic Heart Disease. Available from:

<https://www.ncbi.nlm.nih.gov/books/NBK209964/>

²⁶ Ibid

²⁷ Pedersen OD, Søndergaard P, Nielsen T, Nielsen SJ, Nielsen ES, Falstie-Jensen N, Nielsen I, Køber L, Burchardt H, Seibaek M, Torp-Pedersen C; DIAMOND study group investigators. Atrial fibrillation, ischaemic heart disease, and the risk of death in patients with heart failure. Eur Heart J. 2006 Dec;27(23):2866-70. doi: 10.1093/eurheartj/ehl359. Epub 2006 Nov 13. PMID: 17101637.

<https://pubmed.ncbi.nlm.nih.gov/17101637/>

²⁸ Ramirez-Sandoval JC, Madero M. Treatment of Hyperuricemia in Chronic Kidney Disease. Contrib Nephrol. 2018;192:135-146. doi: 10.1159/000484288. Epub 2018 Jan 23. PMID: 29393124.

<https://pubmed.ncbi.nlm.nih.gov/29393124/>

treatment for when kidney failure occurs and can no longer remove blood and extra fluid from the patient’s body.²⁹

Overall DC-SBM Results

The overall results found by the DC-SBM Clustering seemed to be fairly representative of cardiovascular comorbidities, as most of the diseases clustered together would affect the same part of the system or contribute to the systemic failure in some way or another. However, even though two of the three communities studied in the paper represented the same parent nodes as two of the DC-SBM clusters, the actual subclusters of each community differed, yielding different disease code analysis and results. This is most likely due to a number of reasons— as the partitioning was done differently, this would yield different diseases in each subcluster, especially due to the randomness of the graph model. Additionally, as mentioned previously in section III.4, the “parent node” of each subcluster was chosen by using the highest page ranking of each node, meanwhile the study used the Jaccard Index to rank their nodes. This could cause some variability in the way the nodes are ranked.

As for the real-world application of the results, most of what was found has already been studied and does not offer too much new information as many of the diseases clustered together were already known to coexist in systemic failure. This does however offer insight on how useful and accurate CVC networks can be for further research and analysis in the future.

²⁹ Beecham GB, Aeddula NR. Dialysis Catheter. [Updated 2021 Dec 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from:

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VI. Appendix

Github Repository:

<https://github.com/dafnamargalit/BioNetworks-Project.git>

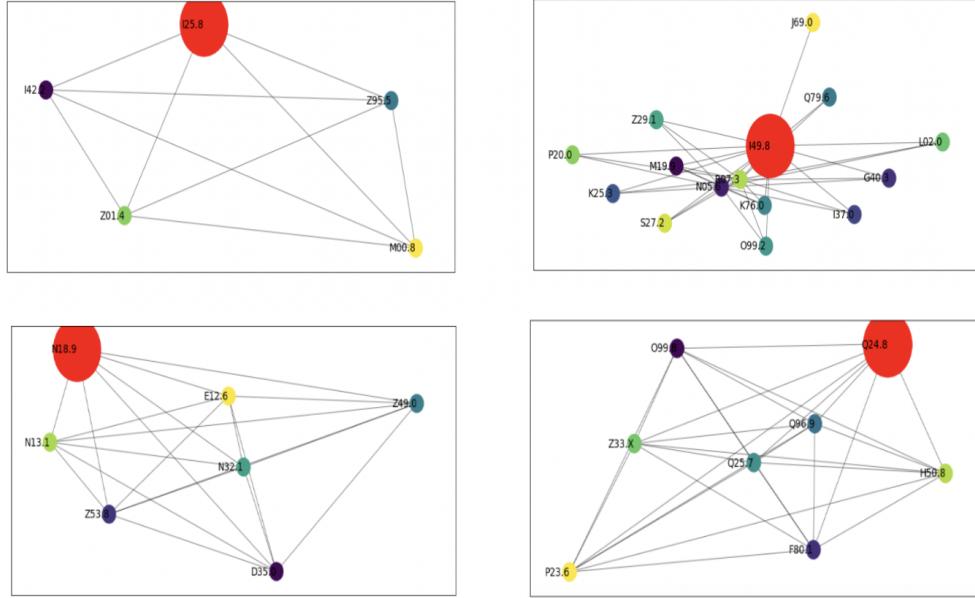


Figure 1: Submodular representation of each top module resulted from the original best simulated partition of Louvain Algorithm. Top left is module 0, top right is module one, bottom left is module 2, and bottom right is module 3.

Sample of Node Data found in “recreated_data.csv”

Name	Clustering Coefficient	Eccentricity	Degree	Current Flow Betweenness Centrality	Shortest Path Betweenness Centrality	Closeness Centrality
Q24.8	0.09412693794	3	491	0.05643088996	0.03584435068	0.5997557003
I49.8	0.0595817451	2	708	0.09117131336	0.07162348099	0.6581769437
Z01.7	0.02207630283	2	1324	0.210433117	0.4845834493	0.9081381011
I09.1	0.2007376933	3	266	0.02398589016	0.008237963771	0.5490122997
N18.9	0.05926084453	3	627	0.09268052275	0.07050263629	0.6349137931

Table 1: Sample of Node data calculated, found in “recreated_data.csv”

Cluster Zero Analysis - This Module is Represented by I25.8 (Other forms of chronic ischemic heart disease)

Subcluster	Number of Nodes	Highest Page Ranked Node	ICD 10 Translation
0	89	I42.2	Other hypertrophic cardiomyopathy
1	111	Z95.5	Presence of coronary angioplasty implant and graft
2	91	Z01.4	Encounter for gynecological examination
3	46	M00.8	Arthritis and polyarthritis due to other bacteria

Cluster One Analysis - This Module is Represented by I49.8 (Other specified cardiac arrhythmias)

Subcluster	Number of Nodes	Highest Page Ranked Node	ICD 10 Translation
0	12	M19.9	Osteoarthritis, unspecified site
1	67	N05.6	Unspecified nephritic syndrome with dense deposit disease
2	4	G40.3	Generalized idiopathic epilepsy and epileptic syndromes
3	3	I37.0	Arthritis and polyarthritis due to other bacteria
4	5	K25.3	Nonrheumatic pulmonary valve stenosis
5	3	Q79.6	Ehlers-Danlos syndromes
6	12	K76.0	Fatty (change of) liver, not elsewhere classified
7	4	O99.2	Endocrine, nutritional and metabolic diseases complicating pregnancy, childbirth and the puerperium
8	2	Z29.1	Encounter for prophylactic immunotherapy
9	2	L02.0	Cutaneous abscess, furuncle and carbuncle of face
10	2	P20.0	Intrauterine hypoxia first noted before onset of labour
11	69	R07.3	Other chest pain
12	6	S27.2	Traumatic hemopneumothorax
13	2	J69.0	Pneumonitis due to inhalation of food and vomit

Cluster Two Analysis - This Module is Represented by N18.9 (Chronic kidney disease, unspecified)

Subcluster	Number of Nodes	Highest Page Ranked Node	ICD 10 Translation
0	45	D35.0	Benign neoplasm of adrenal gland
1	107	Z53.8	Procedure and treatment not carried out for other reasons
2	41	Z49.0	Preparatory care for renal dialysis
3	110	N32.1	Vesicointestinal fistula
4	99	N13.1	Hydronephrosis with ureteral stricture, not elsewhere classified
5	97	E12.6	Malnutrition-related diabetes mellitus with other specified complications

Cluster Three Analysis - This Module is Represented by Q24.8 (Other specified congenital malformations of heart)

Subcluster	Number of Nodes	Highest Page Ranked Node	ICD 10 Translation
0	24	O99.8	Other specified diseases and conditions complicating pregnancy, childbirth and the puerperium
1	23	F80.1	Expressive language disorder
2	58	Q96.9	Turner's syndrome, unspecified
3	46	Q25.7	Other congenital malformations of pulmonary artery
4	40	Z33.X	Pregnant state
5	31	H50.8	Other specified strabismus
6	11	P23.6	Congenital pneumonia due to other bacterial agents

Table 2: Summary tables for each top module, describing their subclusters, number of nodes in each subcluster, ICD-10 code of the node representing each submode, as well as the code translation

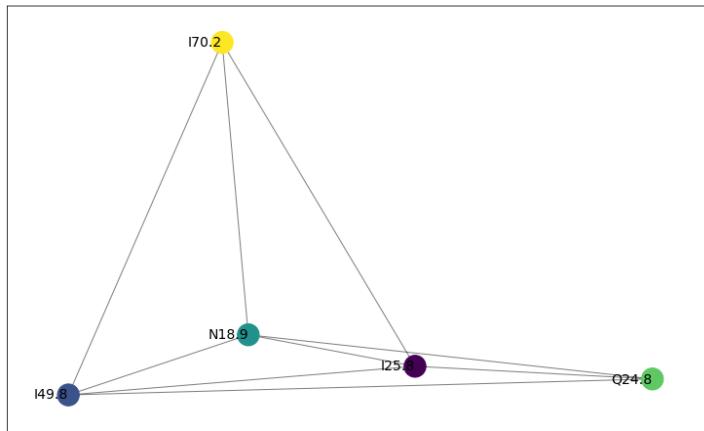


Figure 2: Modular Representation of the Comorbidity Network using Louvain Algorithm partitions. Each module is labeled with its “parent node” or the highest page ranked node in the module.

Summary of Comorbidity Network Clusters

Cluster	Number of Nodes	Highest Page Ranked Node	ICD 10 Translation
0	451	I25.8	Other forms of chronic ischemic heart disease
1	196	I49.8	Other specified cardiac arrhythmias
2	554	N18.9	Chronic kidney disease, unspecified
3	269	Q24.8	Other specified congenital malformations of heart
4	4	I70.2	Atherosclerosis of native arteries of the extremities

Table 3: Summary table of the five clusters returned from the best simulated Louvain

Summary of Comorbidity Network Clusters created with DC-SBM

Cluster	Number of Nodes	Highest Page Ranked Node	ICD 10 Translation
0	110	Q24.8	Other specified congenital malformations of heart
1	335	I49.8	Other specified cardiac arrhythmias
2	192	Z01.7	Laboratory examination
3	619	I09.1	Rheumatic diseases of endocardium, valve unspecified
4	218	N18.9	Chronic kidney disease, unspecified

Table 4: The five communities found and their highest page ranked node.

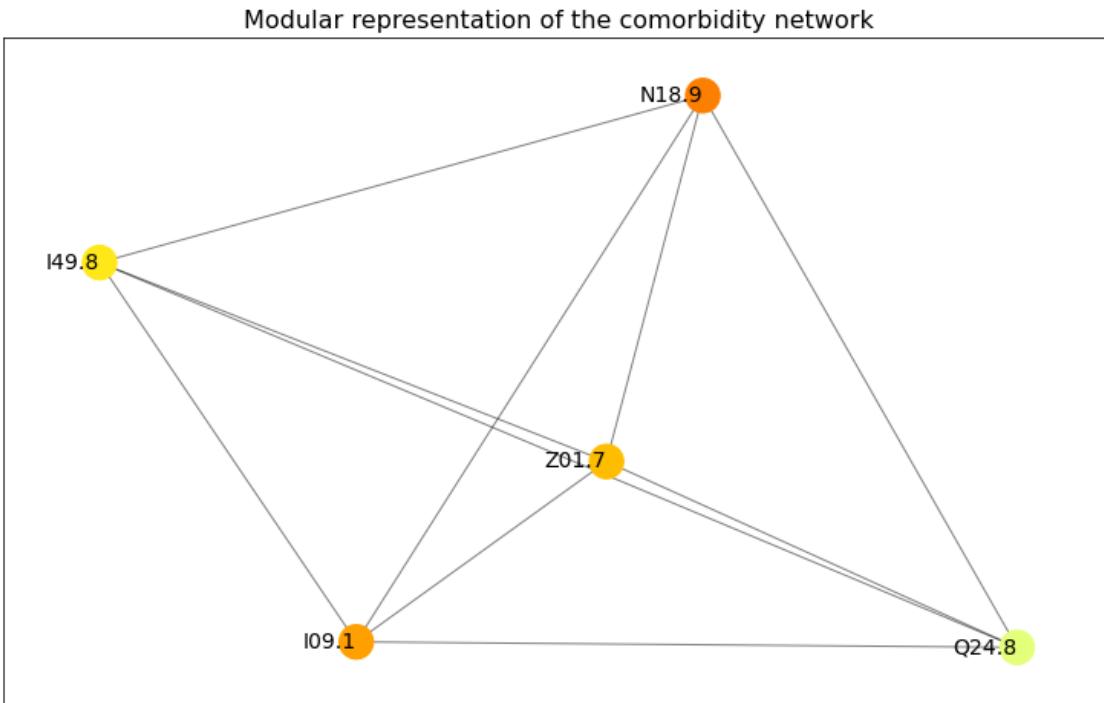


Figure 3: Modular Representation of the Comorbidity Network using the DC-SBM created partitions. Each module is labeled with its “parent node” or the highest page ranked node in the module.

Cluster 0 - Q24.8 (Other forms congenital malformations of heart)

Subcluster	Number of Nodes	Highest Page Ranked Node	ICD 10 Translation
0	25	Q21.1	Atrial septal defect
1	28	Q21.0	Ventricular septal defect
2	30	I27.0	Primary pulmonary hypertension
3	16	Q26.2	Total anomalous pulmonary venous connection
4	10	Q20.8	Other congenital malformations of cardiac chambers and connections

Table 5: The five subclusters found Cluster 0 and their highest page ranked node.

Cluster 2 - Z01.7 (Laboratory examination)

Subcluster	Number of Nodes	Highest Page Ranked Node	ICD 10 Translation
0	50	I48.X	Atrial fibrillation and flutter
1	55	I25.8	Other forms of chronic ischemic heart disease
2	41	I70.9	Generalized and unspecified atherosclerosis
3	42	I24.8	Other forms of acute ischaemic heart disease

Table 6: The five subclusters found Cluster 2 and their highest page ranked node.

Cluster 4 - N18.9 (Chronic kidney disease, unspecified)

Subcluster	Number of Nodes	Highest Page Ranked Node	ICD 10 Translation
0	41	Z49.1	Encounter for fitting and adjustment of extracorporeal dialysis catheter
1	20	E11.2	Type 2 diabetes mellitus with kidney complications
2	32	Z49.2	Encounter for fitting and adjustment of peritoneal dialysis catheter
3	30	Z52.4	Kidney donor
4	21	E79.0	Hyperuricemia without signs of inflammatory arthritis and tophaceous disease
5	19	Z96.0	Presence of urogenital implants
6	16	E14.2	Unspecified diabetes mellitus with renal complications
7	18	I13.1	Hypertensive heart and renal disease with renal failure
8	20	Z99.2	Dependence on renal dialysis

Table 7: The five subclusters found Cluster 4 and their highest page ranked node.

Cluster 1 - I49.8 (Other specified cardiac arrhythmias)

Subcluster	Number of Nodes	Highest Page Ranked Node	ICD 10 Translation
0	58	I10.X	Essential (primary) hypertension
1	5	N04.X	Nephrotic syndrome with minor glomerular abnormality
2	3	Q10.5	Congenital stenosis and stricture of lacrimal duct
3	10	I11.9	Hypertensive heart disease without heart failure
4	28	N87.9	Dysplasia of cervix uteri, unspecified
5	3	N00.9	Acute nephritic syndrome with unspecified morphologic changes
6	4	Z96.1	Hypertensive heart disease without heart failure
7	13	Q61.2	Polycystic kidney, adult type

Table 8: The five subclusters found Cluster 1 and their highest page ranked node

Cluster 3 - I09.1 (Rheumatic diseases of endocardium, valve unspecified)

Subcluster	Number of Nodes	Highest Page Ranked Node	ICD 10 Translation
0	166	I36.1	Nonrheumatic tricuspid (valve) insufficiency
1	8	J86.0	Pyothorax with fistula
2	23	I71.6	Thoracoabdominal aortic aneurysm, without rupture
3	6	C34.8	Malignant neoplasm: Overlapping lesion of bronchus and lung
4	45	Z45.8	Adjustment and management of other implanted devices
5	10	D35.2	Benign neoplasm of pituitary gland
6	8	D81.8	Other combined immunodeficiencies

Table 9: The five subclusters found Cluster 3 and their highest page ranked node

Module	Comorbidity duplex	Common genes	Jaccard index	Enriched pathways
Other specified congenital				Biosynthesis of phenylalanine tyrosine Biosynthesis of tryptophan Biosynthesis of glycosaminoglycan Mineral absorption Nitrogen metabolism Biosynthesis of aminoacids Carbon metabolism Nf-kappa b signaling pathway necroptosis RNAm surveillance Nicotine addiction Pentose-phosphate pathway mRNA surveillance Ribosome biogenesis in eukaryotes Amino acid biosynthesis Carbon metabolism RNA transport Nf-kappa b signaling Neuroactive ligand-receptor interaction Necroptosis Ascorbate and aldarate metabolism Pentose and glucuronate interconversions Steroid hormone biosynthesis Retinol metabolism Porphyrin and chlorophyll metabolism Drug metabolism Chemical carcinogenesis Metabolism of xenobiotics by cytochrome P450 Arrhythmogenic right Ventricular cardiomyopathy
malformations of heart (Q24.8)	Exotropia (H50.1) and Pectus excavatum (Q67.6)	1,292	0.596766744	
	Exotropia (H50.1) and Agenesis of lung (Q33.3)	644	0.37771261	
	Unspecified adverse effect of drug or medication (T88.7)			
	and Intentional self-inflicted injury by hanging, strangulation or suffocation, in an unspecified location (X70.9)	28	0.120689655	

Table 10: Table 3 from the 2020 study showing the Q24.8 comorbidities.³⁰

³⁰ Cruz-Ávila et. al, 2020