University of Twente

Masters Assignment Health Sciences
Faculty of Science and Technology

"The Impact of COVID-19 on the Procedures in the Diagnostic Pathway for Lung Cancer Patients."

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1 Abstract

Background: The Covid-19 pandemic has profoundly disrupted healthcare systems worldwide, including the diagnostic pathways for lung cancer patients. This study aims to visualise and analyse the changes in these pathways in the Netherlands, comparing pre-pandemic and peri-pandemic periods.

Methods: Components from the Dutch Cancer Registery (NCR) and Dutch Hospital Data (DHD), maintained by Netherlands Comprehensive Cancer Organisation (IKNL), are merged to a dataset. The dataset, including 41,310 patients diagnosed with lung cancer from January 2017 to July 2021, are segmented into pre-Covid (Group A), crossover i.e. first contact pre- and clinical diagnosis peri-Covid (Group B), and peri-Covid (Group C) periods, stratified by clinical tumour stage. The analysis focused on diagnostic activities, their frequencies, durations, and transitions within care pathways. Utilising process mining techniques, specifically the heuristic miner algorithm, the sequence of the retrospective cohort data is analysed.

Results: There is a large diversity in the diagnostic pathways of lung cancer. The study identified alterations in diagnostic practices due to the pandemic, such as a reduction in repetitions of diagnostic activities such as X-Thorax scans, and the overall number of activities also decreased. The use of PET scans decreased significantly in group C, but this reduction was less noticeable for stage 4, as PET scans were already infrequently used for these stages before Covid-19. Conversely, the adoption of endobronchial ultrasound (EBUS) increased, particularly for stage 3 patients in groups B and C. Additionally, a higher percentage of patients were diagnosed through the three most common pathways when comparing group A to groups B and C. The lengths of diagnostic paths increased from group A to group B but slightly decreased overall from group A to group C, with fewer outliers.

Conclusion: The study reveals adaptations in the diagnostic pathways for lung cancer patients during the Covid-19 pandemic. Overall, the study underscores the healthcare system's adaptability and the importance of refining diagnostic pathways to balance efficiency, accuracy, and resource allocation during crises like the Covid-19 pandemic.

2 Background

In December 2019, the China Country Office of the World Health Organization (WHO) received a notification regarding multiple instances of pneumonia of unknown etiology. These first cases of Covid-19 quickly spread to other regions, countries, and continents [1]. After the first case was diagnosed in the Netherlands on February 27, 2020, strict social distancing measures and quarantine rules were implemented. The increased pressure on health care and social distancing affected the clinical admissions. As a consequence, healthcare underwent alterations for several months, driven by the quick implementation of new protocols and guidelines [2, 3]. Moreover, in general practitioner (GP) practices, the number of consultations for non-Covid-19 care decreased [4]. This could have caused a delay in the definitive diagnosis of cancer and subsequent treatment. For example, the number of weekly cancer diagnoses (excluding skin cancer) in the Netherlands decreased to 73% and even to 39% for skin cancer, compared to the weeks preceding the Covid-19 outbreak [5]. For lung cancer, which is already the cancer with the highest number of cancer-related deaths in the Netherlands [6], a decrease in pathologically confirmed tumours of the airway was observed from week 12 of 2020 [5]. After this decline, it was feared that these patients would emerge later that year with a higher cancer stage, but the cumulative number of patients with stage 4 was similar to the numbers in previous years. However, there is a visible increase from March 2021 in the number of patients diagnosed with stage 4 of airway cancers (e.g. lung, tracheal, bronchial, laryngeal and thyroid cancer), but it was comparable to 2018 and 2019 [7].
These trends raise questions about the pandemic's exact impact on diagnostic procedures in cancer care. Understanding the changes in the diagnostic pathway is crucial. Investigating these changes will help ensure preparedness and adaptation for future pandemics, enhancing resilience and responsiveness within cancer care systems.

By exploring the patient care pathways (CPW) in the Netherlands, policy makers can assess and identify how to improve current practice bottlenecks in these trajectories. Working to reduce these bottlenecks in the future can minimise waiting times and improve outcomes [8]. A CPW is a structured multidisciplinary care plan that provides a visual overview and aims to translate the recommendations of the clinical practice guideline into clinical care processes [9].
The Netherlands currently does not have a lung cancer screening program [10]. Consequently, asymptomatic lung carcinomas are generally diagnosed by identifying a lung nodule on an X-thorax, ordered for other medical reasons [11]. Most lung cancer patients are diagnosed at an advanced or metastatic stage, as symptoms typically manifest only in these later stages. Consequently, the overall 5-year survival rate for lung cancer patients diagnosed between 2015 and 2021 is mere 25%. [12]. The diagnostic pathway in the Netherlands currently consists of multiple non-invasive techniques, such as positron emission tomography (PET) scans or computed tomography (CT) scans, and invasive techniques such as a bronchoscopy, endobronchial, or ultrasound guided transthoracic biopsy (EBUS-TBNA) [13]. This study aims to visualise the diagnostic track of lung cancer patients along the care pathway, utilising data from the Netherlands Cancer Registry (NCR), a population- based cancer registry hosted by the Netherlands Comprehensive Cancer Organisation (IKNL), and Dutch Hospital Data (DHD). This work aims to find the differences the Covid-19 pandemic has brought on the diagnostic track of lung cancer,

by looking into a possible change of the frequency of the diagnostic activities, the amount of activities per patient, the most common pathways and the duration of the diagnostic process. By employing process mining techniques and clinical big data analysis, patterns can be found within the lung cancer dataset, providing comprehensive insights into diagnostic practices. To visualise these diagnostic patterns, the heuristic miner technique is applied. This process mining method identifies the most frequent patterns and deviations within the patient data. These are shown in a net to show the diagnostic steps, transitions, and decision points encountered.

3 Method

This section provides an introduction to process mining, highlighting the advantages and disadvantages of the heuristic miner algorithm. It also elaborates on the methods used for categorising patients based on Covid-19 periods, outlines the data collection and event log specifications, and details the analytical techniques employed in the study.

3.1 Heuristic Miner in Process Mining

Process mining is a method used to discover, monitor, and improve processes by analysing big data. The foundation of process mining lies in the analysis of event logs, which are essential for identifying trends and patterns within the process data [14]. An event log is a type of dataset that captures a sequence of events or activities over time and must include key attributes: an activity, a timestamp, and a case identification. The healthcare industry generates a large amount of data detailing patient healthcare trajectories. These data can be leveraged to analyse patient pathways to discover the true sequence of activities within a process [15]. The discovery of clinical pathways can be achieved effectively using the heuristic miner technique [16]. An advantage of the heuristic miner technique is its ability to handle noisy data effectively, filtering out irrelevant or erroneous activities while identifying significant patterns. Using cutoff values, the algorithm can manage noise while still highlighting infrequent behaviour [15]. Additionally, this technique is relatively simple and fast compared to more complex process mining techniques, making it suitable for large datasets and even real-time analysis [17]. However, the technique has its disadvantages as well. The results can be highly sensitive to the chosen parameters, such as cutoff values, which require careful tuning to avoid missing important patterns or including too much noise [18].
Taking all these points into consideration, the heuristic miner algorithm has been chosen as the primary analytical method. The event log data is processed through this algorithm to create heuristic nets for different patient groups based on their cancer stage and whether their treatment occurred during the Covid-19 period or before. Heuristic nets show each activity as a node. These nodes are connected with arrows, indicating the frequency of a certain flow between the nodes.

3.2 Definition of Covid Groups

To find the actual effects that the pandemic had on the diagnostic pathway of lung cancer, there is a focus on the variation between these groups for the pre-Covid and peri-Covid period, which are defined as January 2017 to 29 February 2020 and 1 March 2020 to July 2021, respectively. In this research, no distinction was made between different Covid waves. Since the diagnostic pathway of patients can consist of multiple events, it cannot be defined by just one date. There is a possibility that there are patients who have their initial consultation in the pre-Covid and the clinical diagnosis in the peri-Covid period. In order to make a proper division between the periods, the patients are split into three groups; group A, for whom the entire diagnostic pathway is in the pre-Covid period, group B, for whom the pathway crosses over the Covid barrier, and group C, with only peri-Covid patients. The analysed period for each patient begins at the first consultation and ends at the initiation of treatment. If no treatments are administered, the period ends at the time of diagnosis.

3.3 Data Collection and Event Log Specifications

This retrospective cohort study included patients over 18 years of age who were diagnosed with Small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) lung cancer between January 2017 and July 2021 in one of the 69 participating Dutch hospitals. Based on pathological notifications through the Dutch pathology archive (PALGA), and hospitals discharge notifications, data managers transfer relevant information from the patient files into the NCR. This data is maintained by IKNL. The cohort of patients from the participating hospitals is connected to the DHD to obtain detailed hospital information about a total of 149 different diagnostic activities. Examples include all radiological examinations of the thorax, bronchoscopies, and several oncological PET scans. Each activity is meticulously documented along with its corresponding date, though the exact time on the day is not specified. The minimum requirements for an event log for process mining (activity, timestamp, and case ID) correspond to the following: diagnostic activity, the corresponding timestamp, and patient ID. Furthermore, since this study focuses solely on the diagnostic process, all activities after the diagnostic date were not used.

The complete event log is then prepared for the analysis. All patients with multiple tumours in the inclusion period are identified and marked for removal in subsequent analyses. This step is necessary because the diagnostic process differs for patients with recurrent tumours and the merged dataset does not provide the possibility of distinguishing whether a diagnostic step was part of the pathway for a first or any subsequent tumours. Furthermore, patients are classified into Covid-19 groups A, B, or C based on their timing of diagnosis in relation to Covid period as explained in Section 3.2. When there is difficulty with the date sequence, since the treatment date precedes the date of diagnosis, the patients are removed from the event log. Subsequently, patients are classified according to their respective clinical cancer stages. Cancer stages 0, 1 and 2 are grouped together because both stage 0 and 2 hold relatively smaller populations [19]. By including this group in stage 1, a larger group was made, thus more can be said about the differences between the advanced and earlier stages [20], while stages 3 and 4 are analysed separately. Patients with an unknown clinical stage are excluded from the dataset. The selection of patient groups is visualised in Figure 1, using the Mermaid Chart extension for Visual Studio Code [21]. The dataset preparation is performed using Stata/SE 17 [22].

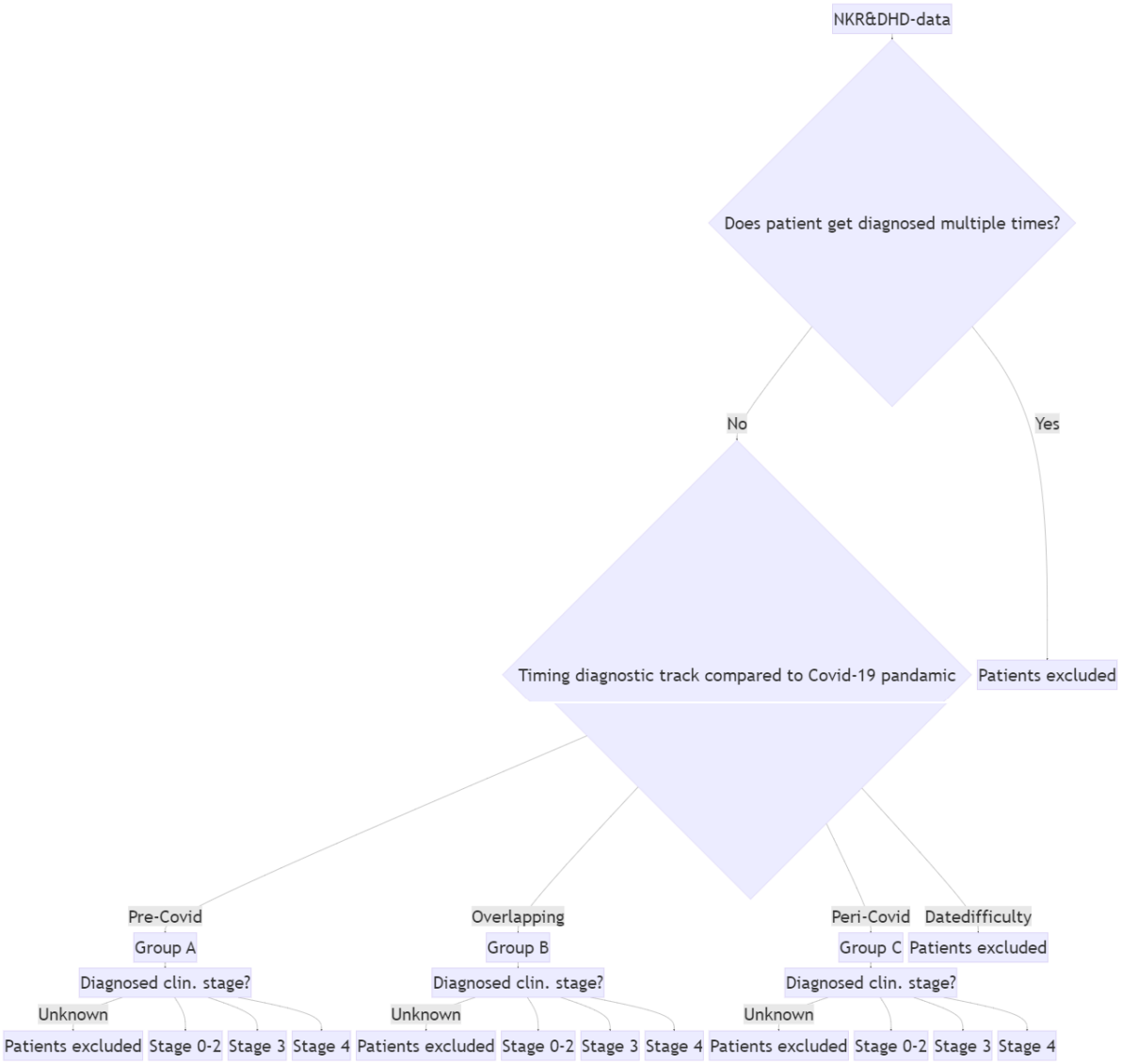


Figure 1: *Selection and Division of Patient Groups, *Date difficulty: Treatment date precedes the date of diagnosis*

3.4 Analysis

For the analysis, a code is scripted in Python 3.12, specifically leveraging the PM4py package, which is designed for process mining [23]. After the descriptive analysis of the patient group, the results continues in three sections: frequency analysis, pathway variability analysis, and heuristic net analysis.

Frequency Analysis
To understand the diagnostic pathways, the frequency of various diagnostic activities is analyzed. This metric helps identify common diagnostics and variations between different Covid groups and stages of cancer, enabling a comparison of their frequencies. The frequencies of the diagnostic activities are plotted on a graph for each stage group, with the

Covid periods in chronological order on the y-axis. The frequencies are approached from two angles: firstly, the frequency rate, which shows the frequency of a specific diagnostic activity, divided by the patient population. Secondly, the patient percentage, which shows which percentage of the patient group receives a certain diagnostic activity.
Additionally, the number of diagnostic activities per patient is calculated. This metric provides insight into the complexity and intensity of the pathway, revealing how different Covid groups and stages may require varying levels of intervention. While the first part of the frequency analysis provides information on the use of specific diagnostic activities, the number of activities sheds light on the use of resources per patient group. Understanding these trends can aid in resource planning and management.

Pathway Variability Analysis
To gain better insight into how frequencies form a diagnostic pathway, the number of pathway options, referred to as variations, are calculated. From these variations, the top three pathways for each Covid period and stage group are identified. Focusing on the most common pathways reveals key patterns consistent across many cases.
Lastly, the duration of all diagnostic paths, from the first consultation until the diagnosis, is analysed per group and stage. This metric assesses the timeliness of the diagnostic process, which is crucial for early detection and treatment. The duration is visualised using various boxplots. Significant outliers can greatly impact the clarity of these boxplots, potentially necessitating the filtering out of certain data points for better visibility.

Heuristic Nets Analysis
In lung cancer diagnostics, the complexity and diversity of patient pathways present challenges and opportunities. Heuristic mining, a process mining technique, helps us uncover these pathways by analysing event logs from patient records. The reasoning, advantages and disadvantages of this algorithm are previously mentioned in Subsection 3.1. The event log inherently contains noise that has to be dealt with. Noise in a dataset refers to any irrelevant or meaningless data that can distort or obscure the actual patterns and information that the data set is meant to convey. In this case, it can manifest in several ways, such as missing values, outliers, incorrect timestamps, and erroneous event sequences. To deal with noise, a dependency threshold is chosen, which sets a cut-off percentage for how strong the dependency between two activities must be for it to be included in the heuristic net. Suppose activity A occurs 100 times, and it is directly followed by activity B 50 times, this means the dependency is 0.5. Dependencies below the chosen threshold are considered relatively weak and are excluded from the final process model. A lower threshold does capture more of the diversity within the event log, providing a comprehensive view of patient pathways.
To further reduce complexity of the nets, the number of activities can be reduced by only showing the top 10 most frequent activities in the nets, or by aggregating the activities. Aggregation involves merging smaller units of data into larger units, in this case specific diagnostic steps into broader terms. As different steps might serve similar purposes in the diagnostic pathway, this simplification makes it easier to identify general trends and reduces the complexity of the analysis.
The aggregation of this heuristic net is based on the SNOMED CT Browser categorisation system hosted and maintained by the NHS Digital as can be seen in Table 4 in the Appendix [24].

4 Statistical Analysis & Results

4.1 Descriptive Statistics

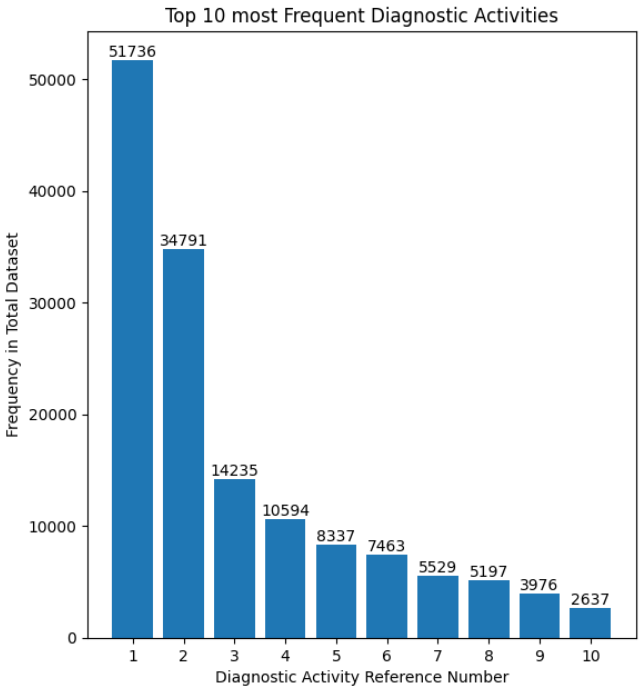
On the whole, the merged dataset results in 530,926 activities over 58,817 patients. The minimum requirements for an event log for process mining (activity, timestamp, and case ID) correspond to the following: diagnostic activity, the corresponding timestamp, and patient ID. After merging, for 4,241 out of 530,926 activities there was no available activity date and as those could not be used for the analysis, they are removed from the dataset. Furthermore, since this study focuses solely on the diagnostic process, all activities after the diagnostic date were not used. This resulted in 193,927 remaining activities. The exclusion of these activities also led to the exclusion of 6,661 patients (11.32%). However, since these patients did not have timestamps in the diagnostic track, they were not included in the starting point of the dataset.
The complete event log of 45,958 patients is then prepared for the analysis. All patients with multiple tumours in the inclusion period are identified and marked for removal in subsequent analyses, causing 1,232 patients to be excluded, which account for 2.68% of the patients. In 709 cases, there is difficulty with the date sequence, since the treatment date precedes the date of diagnosis. These patients are removed from the dataset. There is an unknown clinical stage for 2,223 patients from all groups in total, which is 4.84% from the collected patient data. This results in a total of 41,310 (out of 45,958) patients included in the research.

	Group A	**Group B**	**Group C**
Demographic Characteristics			
Number of patients	31,566	794	11,173
Age, mean (SD, range)	69.30 (9.95, 18-102)	68.06 (9.74, 20-89)	69.46 (9.61, 18-98)
Gender, n (%)			
Male	17,423 (55.20)	433 (54.53)	6,047 (54.12)
Female	14,143 (44.80)	361 (45.47)	5,126 (45.88)
Clinical Characteristics			
Cancer stage, n (%)			
Stage 0-2	8,702 (27.57)	325 (40.93)	2,895 (25.91)
Stage 3	6,864 (21.74)	174 (21.91)	2,300 (20.59)
Stage 4	16,000 (50.69)	295 (37.15)	5,978 (53.50)

Table 1: *Baseline Demographic and Clinical Characteristics Population*

4.2 Frequency Analysis

Understanding the diagnostic pathway involves looking into the frequency of various diagnostic activities. Figure 2 shows the most frequent activities on the diagnostic track of all included patients in the analysis.



Nr.	Diagnostic Activity
1	Radiological examination thorax including fluoroscopy
2	Computed tomography of the thorax, heart, and great vessels
3	PET whole body - oncology
4	Bronchoscopy - diagnostic including biopsy, curettage, etc.
5	Echo bronchoscopy (EBUS) including possible biopsies
6	CT scan only prior to PET or SPECT
7	CT of the brain and/or skull
8	Heart - echocardiography
9	Radiological examination of the thorax in 2 directions
10	Pleura - puncture - diagnostic

Figure 2: *10 Most Received Diagnostic Activities*

To compare these frequencies per subgroup, the most frequent activities are separated in stage groups and analysed over the different Covid groups in time. The exact frequency rates and percentage values of patients can be found in the Appendix in Figures A.1, A.2, and A.3.

Figure 3, which shows the frequency comparison for stage 0-2, reveals quite a few notable changes. For example, the number of patients who received a full-body PET as part of their diagnostic pathway declines from 46% of patients to only 13%. The absolute amount of PET scans also declined from 0.60 per patient to only 0.19 per patient. Additionally, while 33% of patients in group A receive a CT prior to PET / SPECT, in group C this is only 10.5% of cases.

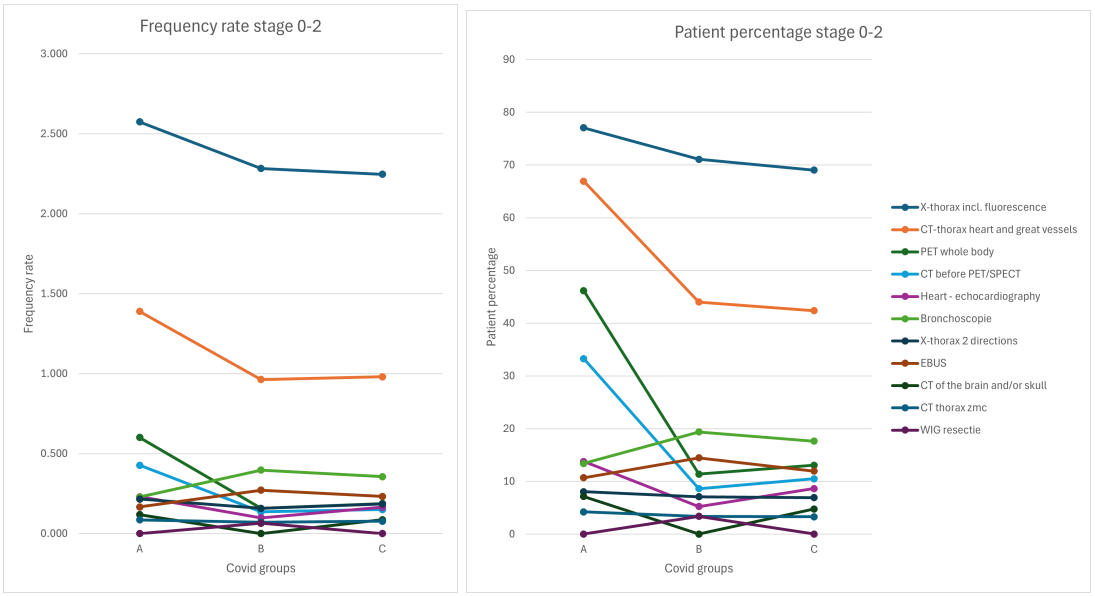


Figure 3: *Frequency Comparison Stage 0-2, Stratified by Covid Group*

For patients diagnosed in stage 3 of lung cancer (Figure 4), it is noticeable that fewer X-thorax, CT-Thorax, PET scans, CT scans before PET/SPECT and echocardiography are administered in group C compared to group A, both in frequency rate and patient percentage. However, more bronchoscopy, EBUS and echos were performed in group C.

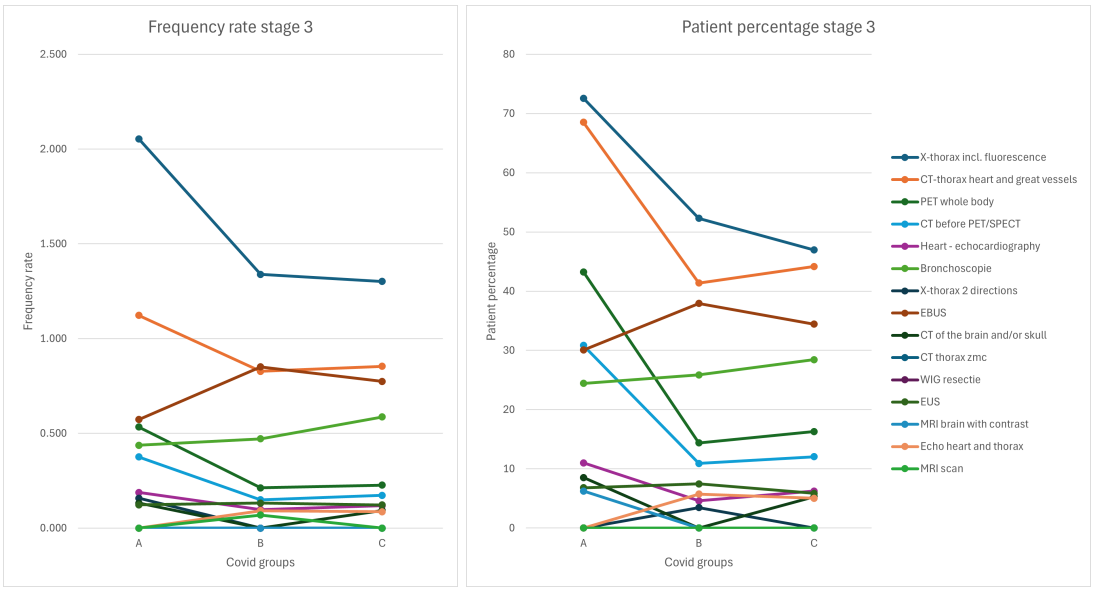


Figure 4: *Frequency Comparison Stage 3, Stratified by Covid Group*

Patients diagnosed with stage 4 lung cancer (Figure 5) give results similar to those of stage 3, which means the overall frequency rate and patient percentage from group A to group C decline for X-thorax, CT-Thorax, PET scans, CT scans before PET/SPECT

and echocardiography, but increase for bronchoscopy, EBUS, and echos. However, PET scan does not decline as much for this stage compared to stage 0-2 and 3, because it was comparatively not used as often before Covid. Another difference is for the EBUS, that while both usages rise from group A to group C, it is used a lot more often for stage 3, than for stage 4.

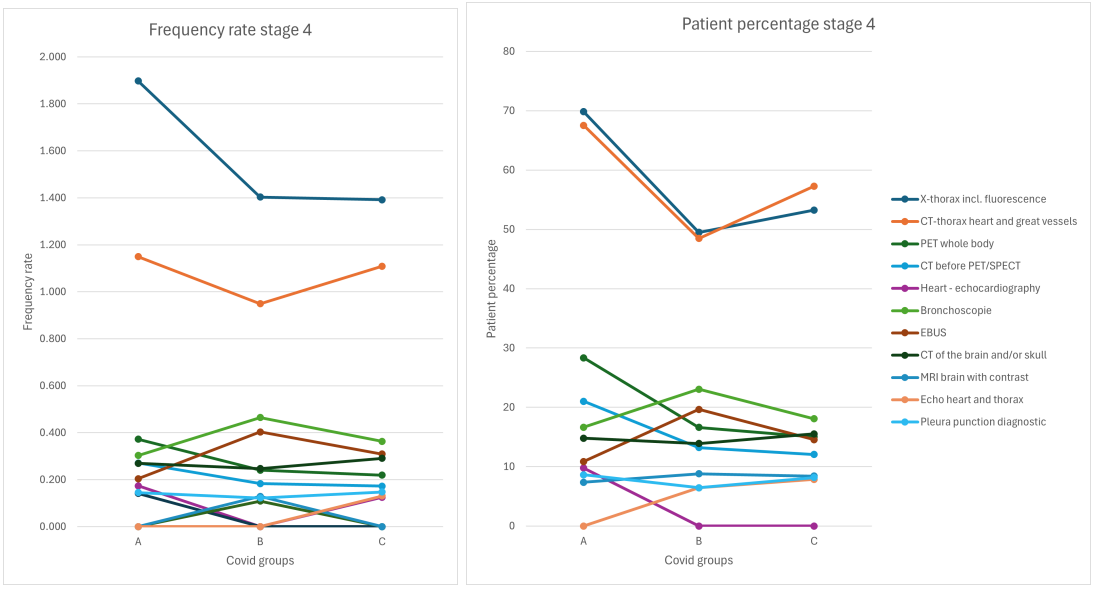


Figure 5: *Frequency Comparison Stage 4, Stratified by Covid Group*

Additionally, the amount of diagnostic activities per patient are calculated and shown in Figure 6. The overall number of activities for a patient in the diagnostic track, which stretches from the moment of the first consult to the date of diagnosis, decreases from group A to group C. Additionally, the variability in the number of activities (as shown by the smaller whiskers in boxplots) is lower for group C, indicating more consistent diagnostic processes for this group.

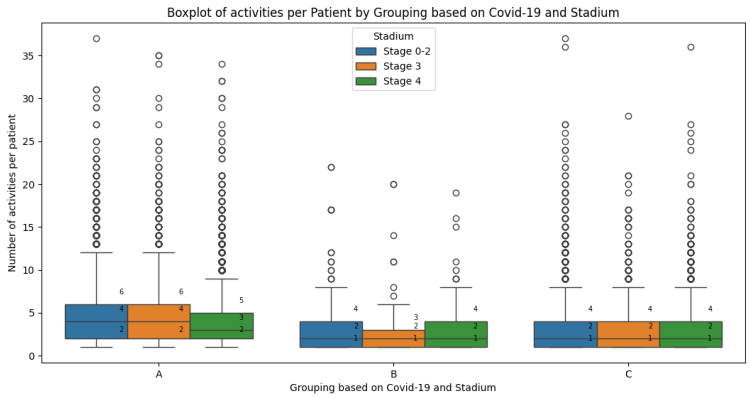


Figure 6: *Number of Activities per Patient in Diagnostic Track, Stratified by Period and Tumour Stage*

4.3 Pathway Variability Analysis

Table 2 shows the number of pathway variations and the number of patients per Covid group and cancer stage group. Notably, smaller patient subgroups for Covid group B display more pathway variations. For instance, Covid group B, stage 4, with the highest number of variations (185), has only 295 patients. Similarly, Covid group B, stage 3 shows 96 variations among 174 patients. This trend suggests that these smaller groups are more heterogeneous and may be less representable. However, for all subgroups a large variation can be found, with Covid group C, stage 4 showing the smallest variation of on average (5,978/2,072) 2.89 patients per pathway. Overall, no pattern can be found for the number of path variants when comparing group A to group C.

Covid Group	Cancer stage	Patients	Path variants
Group A	Stage 0-2	8,702	4,365
Group A	Stage 3	6,864	3,353
Group A	Stage 4	16,000	5,998
Group B	Stage 0-2	325	169
Group B	Stage 3	174	96
Group B	Stage 4	295	185
Group C	Stage 0-2	2,895	1,060
Group C	Stage 3	2,300	858
Group C	Stage 4	5,978	2,072

Table 2: *Unique Path Variants, Stratified by Period and Tumour Stage*

In Figure A.4 up to A.12 in the Appendix the three most common pathways for each Covid and cancer group are visualised. Table 3 shows a summary of the three most common paths for all 9 subgroups. The most common diagnostic activities are shown on the left in alphabetical order, path number 1, 2 and 3 are respectively the first, second, and third most common paths in that subgroup. The sequence of the activities is shown with numbers. Below each path, the number of patients that get diagnosed via that path and the corresponding percentage that is of the total subgroup are displayed.
When comparing all groups, it can be found that the diagnostic pathway with a single X-Thorax is always the most common pathway, except for group C stage 3, where one diagnostic activity, the EBUS, is the most common pathway. Furthermore, an increase in the usage of the most common pathways can be seen for group B and C, compared to group A, implying more patients get diagnosed via the most common pathways peri-Covid. What is also notable is that when comparing stage 3 between groups, for groups B and C, receiving an EBUS is one of the most common diagnostic methods, while it is not in group A.

Group A	Stage 0-2			Stage 3			Stage 4		
Entering hospital	8,702			6,864			16,000		
Nr of total variants	4,365			3,353			5,998		
Path nr:	1	2	3	1	2	3	1	2	3
Bronchoscopy						1			
CT Thorax, heart and large veins		1	1		1	2		1	1
X-thorax	1	2		1	2	3	1	2	
Patients via this path	673	328	222	414	289	150	1,202	1,010	685
% of patients via this path	7.73%	3.77%	2.55%	6.03%	4.21%	2.19%	7.51%	6.31%	4.28%

Group B	Stage 0-2			Stage 3			Stage 4		
Entering hospital	325			174			295		
Nr of total variants	169			96			185		
Path nr:	1	2	3	1	2	3	1	2	3
Bronchoscopy			1						1
CT Thorax, heart and large veins		2				1		1	
EBUS					1				
X-thorax	1	1		1			1	2	
Patients via this path	58	15	17	21	20	9	25	14	14
% of patients via this path	17.85%	4.62%	5.23%	12.07%	11.49%	5.17%	8.47%	4.75%	4.75%

Group C	Stage 0-2			Stage 3			Stage 4		
Entering hospital	2,895			2,300			5,978		
Nr of total variants	1,060			858			2,072		
Path nr:	1	2	3	1	2	3	1	2	3
Bronchoscopy						1			
CT Thorax, heart and large veins			1					1	1
EBUS				1					
X-thorax	1	1&2	2		1		1		2
Patients via this path	470	150	136	209	209	132	544	399	358
% of patients via this path	16.23%	5.18%	4.70%	9.09%	9.09%	5.74%	9.10%	6.67%	5.99%

Table 3: *Three Most Common Pathways, Stratified by Period and Tumour Stage, with Indicated Sequence per Path*

In Figure 7 the duration in days of all diagnostic tracks, from the first consult to the date of diagnosis, are visualised in boxplots. These are firstly separated by Covid groups o.a. A, B, and C and secondly by cancer stage. Due to high outliers, the upper 1.5% was filtered out of each subgroup to make the boxplot more readable. The negative duration values are included in the boxplot, but are set to zero.
When comparing for stage 0-2, group A shows a median of 16, with upper and lower quartiles of 34 and 4 days, respectively. All these values increase for group B and level out to a median of 17, and upper and lower quartiles of 32 and 7 for group C.
For stage 3, the diagnostic track is significantly longer for group B, but overall it goes down slightly from group A to group C. There are also less extreme outliers for group C, compared to group A.

For stage 4, a similar variation to stage 3 can be seen. Group B shows a much longer diagnostic track for all values and also more outliers, but overall from group A to group C the diagnostic track becomes slightly shorter.

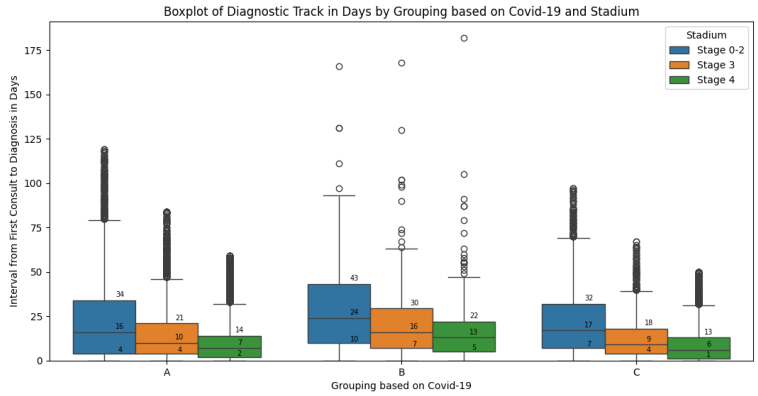


Figure 7: *Days of Diagnostic Track per Patient, Stratified by Period and Tumour Stage*

4.4 Heuristic Net Analysis

It has been found that setting a lower threshold results in a heuristic net that is not visible due to excessive complexity. Therefore, a higher threshold must be selected. Through trial and error, a threshold of 0.8 was chosen, but even this high threshold results in a heuristic net that remains insufficiently visible due to excessive complexity. In the Appendix in Figure A.13 an example of the heuristic net is shown for patients in group A, the pre-Covid group, and cancer stage 0-2. Since they are too complicated to derive information from, the number of visible activities needs to be reduced. This provides nets that are less detailed but significantly more comprehensible. Two options are only working with the top 10 most frequent activities, as shown in Section 4.4.1, or aggregating the diagnostic activities, as done in Section 4.4.2.

4.4.1 10 Most Frequent Activities

In Figure 8 only the top 10 most frequent activities for group A, stage 0-2 are shown in this heuristic net. The sequence of activities can now be deduced, revealing that 4,109 patients, which is 47.22% of this group, receive an X-Thorax as their first treatment. The final diagnosis is made with this diagnostic activity for 4,727 patients and for 4,131 patients another X-Thorax is necessary. Another likely first activity is CT of the thorax, heart, and big veins, with 1,745 patients (20.05%). However, patients do not get their diagnosis solely from this scan. 4,025 patients need an additional X-Thorax after this, 1,466 patients require a brain and skull CT.
For the same stage in group C, the analysis shows that X-Thorax is again visited very often as the first diagnostic activity, 1,481 times, equal to 51.16% (details can be seen in Figure A.14 in the Appendix). 1,343 patients get their diagnosis directly from the X-Thorax. Similarly as the frequency results in Section 4.2 revealed, for Covid group A and C, stage 3, the EBUS shows a higher usage than for stage 0-2 group A (Figure A.15, A.16 in the Appendix). The repetition of the X-Thorax is also lower in group C (426 of 1,751 scans),

compared to group A (2,284 of 8,676 scans). The same difference can be found for stage 4, where the repetition of this scan is 4,367 out of 18,082 for group A, while it is at 1,017 out of the 4,722 scans for group C (Figure A.17, A.18 in the Appendix).

Figure 8: *Heuristic Net with 10 Most Frequent Activities for Group A, Stage 0-2*

4.4.2 Aggregation of Diagnostic Activities

In order to simplify the dataset in another manner, the different diagnostic steps are aggregated. In Figure 9, Covid group A, stage 0-2, the heuristic net once again shows the large variability in the pathways. However, it is clear that the X-Thorax, CT-Thorax, PET scan and bronchoscopy are visited the most frequently from different previous diagnostic activities. Similar results can be seen for Covid group C, with the same stage group, as shown in Figure A.19 in the Appendix. For stage 3 group A (Figure A.20, shown in the Appendix), the PET scan is used with a similar frequency compared to stage 0-2 group A, but is used way less in stage 3 group C (414 times) in Figure A.21 in the Appendix.

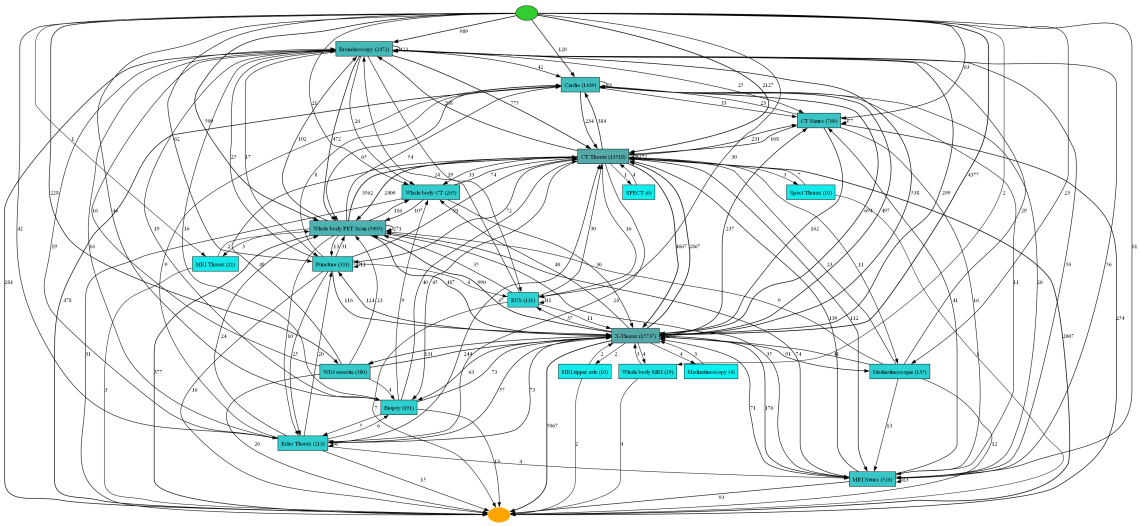


Figure 9: *Heuristic Net with Aggregated Activities for Group A, Stage 0-2*

5 Discussion

5.1 Interpretation of results

This work aims to find the differences the COVID-19 pandemic has brought on the diagnostic track of lung cancer by examining changes in the frequency of diagnostic activities, the number of activities per patient, the most common pathways, the duration of the diagnostic process and the analysis of heuristic nets. Several key results emerged from this study, summarised in bullet points below, followed by a detailed explanation of each finding.

- There is a large diversity in the diagnostic pathways of lung cancer.
- During the Covid-19 pandemic there was a reduction in repetitions of diagnostic activities such as X-Thorax scans. The overall number of activities also decreased.
- The PET scan is used way less in group C, but the decrease in use is not as noticeable for stage 4, because comparatively it was not used as often before Covid.
  The adoption of endobronchial ultrasound (EBUS) increased, particularly for stage 3 patients in groups B and C.
- A higher percentage of patients are being diagnosed through the three most common pathways when comparing group A to groups B and C.
- The lengths of diagnostic paths got longer from group A to group B, but overall from group A to group C got slightly shorter, with less outliers.

The diversity in lung cancer pathways is probably driven by differences in patient characteristics, comorbidity, and symptoms, resulting in unique diagnostic activities for each subgroup. Hence, variability in pathways could reflect individualised diagnostic approaches. In contrast, it can increase the complexity and length of the diagnostic process, leading to longer waiting times for diagnosis and treatment. The need for diverse materials and equipment could strain hospital resources and require more training for staff, potentially increasing costs and the risk of errors.

Prior to Covid-19, there was a high reliance on repeated X-Thorax scans, indicating thorough but potentially redundant diagnostic processes. During the peri-Covid period, there was a noticeable reduction in repetitions and reliance on X-Thorax, suggesting streamlined processes and adaptations to resource constraints. Which also raises questions if some diagnostic activities have been redundant all along. The overall number of activities in the diagnostic pathway decreases from group A to group C, with group C showing less diagnostic activities and possibly more efficiency in the diagnostic processes during the peri-Covid period.

Despite the variability, apparent essential diagnostics such as X-Thorax, CT-Thorax, PET scans, and the bronchoscopy are applied in all subgroups. The peri-Covid reduction in all diagnostic activities might reflect an adaptation to fewer in-person visits or improved diagnostic protocols that were developed in response to the pandemic. Healthcare resources, including personnel and extensive diagnostic equipment, have been limited. To minimise patient exposure to Covid-19, clinical guidelines may have been adjusted to prioritise less invasive and essential diagnostic procedures, reducing the use of more intensive diagnos-

tics. This is also suggested by the European Society for Medical Oncology (ESMO) that present a structured proposal for the management of lung cancer, comprising three levels of priorities [25]. Additionally, patients' fear of contracting Covid-19 in healthcare settings could have added to a decreased use of imaging services.

The steep decrease of the PET scans from stage 0-2 and 3 in group A to C, compared to the slight decrease from group A to C for stage 4, may be attributed to resource allocation to more severe cases during the Covid-19 pandemic. Another example of how diagnostic pathways have been adjusted to match available resources and clinical needs is the use of endobronchial ultrasound (EBUS). It is notable that for stage 3 cancer patients in group B and C, the EBUS is in the top three most common pathways, whereas in group A it is not. EBUS and bronchoscopy also proved to be increasingly used in Section 4.2. EBUS involves inserting a tube with an ultrasound probe through the mouth to examine the airways [26]. EBUS, often paired with transbronchial needle aspirations (TBNA), is proven highly sensitive, specific, and safe, and is recommended for patients with CT nodes over 1 cm or PET-positive mediastinal nodes. [27]. The increased use of EBUS during Covid-19 could be attributed to several factors. The pandemic necessitated the adoption of more precise and minimally invasive diagnostic techniques to reduce the risk of complications and the need for multiple procedures. As EBUS provides direct visualisation and tissue sampling, prioritising them for their ability to provide immediate and detailed information. Additionally, there have been advancements in the availability and familiarity with EBUS technology over time, making it a more common choice during the Covid-19 period. Integrating EBUS-TBNA into standard diagnostic protocols could leverage these benefits for future patient care.

Section 4.3 highlights the trend of a higher percentage of patients being diagnosed through the three most common pathways when comparing group A to groups B and C, despite not showing more path variations. This could partially be explained by a change in diagnostic focus with a greater reliance on established pathways. In addition, reduced non-Covid-related medical consultations might have led to fewer incidental findings, making diagnoses more likely through deliberate pathways. In contrast, some research suggests the opposite: "Due to the overlap of SARS-CoV-2 symptoms with those of lung cancer, new lung cancer diagnoses were accounted for in many of our patients", as mentioned by Mangone et al. [28], which researched the influence of Covid-19 on new lung cancer diagnoses in Northern-Italy. Although the total number of diagnoses decreased [5]. This statement might mean that the effects of the previously mentioned decrease of lung cancer patients may be even greater than initially thought.

When comparing the duration of patients diagnoses for stages 0-2, there is an increase in the length of the diagnostic track from group A to group B. Only a small increase in the median diagnostic track duration in group C compared to group A can be found, although the differences are not substantial. This suggests that despite the pandemic's pressures on healthcare systems, the early-stage diagnostic process maintained a level of consistency. Similar results are found by Helsper et al. [29]; the hospital diagnostic track was determined to be around 18 days during the first Covid-19 wave for lung cancer, which was similar to the pre-Covid-19 period. However, slightly varying results are found for more advanced cancers (stages 3 and 4), there is an increase in the diagnostic track in

group B, followed by a reduction in duration in group C. This reduction makes the diagnostic track slightly shorter in group C, compared to group A. The presence of fewer extreme outliers in group C compared to group A indicates improved consistency and potentially a more streamlined diagnostic process as healthcare systems adapted over time.

5.2 General limitations

5.2.1 Exclusion of patients

The exclusion of patients on numerous levels likely introduces a selection bias that can affect the generalisability of the study findings. The reasons for these exclusions, whether due to incomplete records, missing key variables, or other criteria, must be carefully considered.
Additionally, quite a few patients had questionable data, such as intervals between dates that did not make sense. For instance, there were cases where the interval between the first consult and the diagnosis date was negative, suggesting that the diagnosis date was before the first consult.

5.2.2 Pseudonymised dataset

The pseudonymisation of data presents challenges, particularly when working with dates, only the diagnostic date could remain in month/year format. For process mining, where an exact timestamp is required, all diagnostic dates were set to the first of the month, and the approximate date of each activity was calculated, using the interval in days between the activity and diagnosis. This adjustment introduces potential errors in the sequence of diagnostic activities for the heuristic nets, as the actual dates can vary by up to one month.

5.2.3 Heuristic Net

Displaying data in a heuristic net for a large dataset, such as patients with lung cancer, presents several challenges and disadvantages. While the heuristic net offers valuable insights into the diagnostic pathways for lung cancer patients, it presents challenges when it comes to comparing these pathways with each other. The complexity and variability inherent in individual patient pathways make it difficult to standardise comparisons. Differences in medical history, presentation of symptoms, and treatment responses further complicate this task. Consequently, although heuristic nets are useful for visualising potential pathways, their utility in comparative analysis is limited.
Another significant issue is the threshold for visibility. In this study, a threshold of 0.8 had to be set to make each subset even slightly visible. Setting a high threshold like 0.8 can result in the exclusion of less common but potentially important variations in patient pathways. There is a risk of drawing misleading conclusions about the efficiency and effectiveness of healthcare care processes. Rare events or less common pathways might be indicative of systemic issues or areas needing attention, but are not highlighted due to their lower frequency.
Even with a high threshold, a large dataset can result in a complex and cluttered visualisation. This can diminish the clarity and usability of the visualisation, making it challenging for stakeholders to extract actionable insights. As Namaki Araghi et al. [30] states, the thresholds have to be determined arbitrarily, which is a major structural challenge for the

classic heuristic miner algorithm.

To address the visualisation issues, the initial heuristic net is subsequently refined through only showing the top 10 activities. Another method used is the aggregation of activities into broader categories, showing only different types of activities in groups. These techniques significantly reduced complexity and enhanced focus on the most critical steps in the patient pathways. This approach helps mitigate visual clutter and makes the heuristic net more interpretable.
The simplification of heuristic nets come with notable drawbacks. It leads to loss of detail but also introduces bias by overemphasising common pathways. Aggregating activities into broader categories also results in a loss of granularity, as the aggregation of distinct activities will make it harder to pinpoint specific problems within the patient care process.

6 Conclusion

The study reveals adaptations in the diagnostic pathways for lung cancer patients during the Covid-19 pandemic. Diagnostic activities decreased overall, with a notable reduction in repeated X-Thorax scans, reflecting streamlined processes due to resource constraints. This raises questions about whether some diagnostic activities have been redundant all along. Diagnostic pathways have also been adjusted to match clinical needs as each cancer stage experiences different changes to their respective diagnostic paths. The study also shows a greater reliance on the established pathways. Despite the pandemic's pressures on healthcare systems, the diagnostic processes maintained a level of consistency in their duration from the first consult to the clinical diagnosis. Overall, the study underscores the healthcare system's adaptability and the importance of refining diagnostic pathways to balance efficiency, accuracy, and resource allocation during crises like the Covid-19 pandemic.

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A Appendix

A.1 Frequency Comparison Tables

	Group A, stage 0-2 (8702 patients)		Group B, stage 0-2 (325 patients)		Group C, stage 0-2 (2895 patients)	
	Frequency rate	Prevalence	Frequency rate	Prevalence	Frequency rate	Prevalence
X-thorax incl. fluorescence	2.575	77.06	2.283	71.08	2.247	69.02
CT-thorax heart and great vessels	1.389	66.93	0.963	44	0.981	42.38
PET whole body	0.601	46.18	0.157	11.38	0.187	13.06
CT before PET/SPECT	0.427	33.28	0.135	8.62	0.150	10.5
Heart - echocardiography	0.230	13.79	0.098	5.23	0.164	8.64
Bronchoscopie	0.228	13.39	0.397	19.38	0.355	17.62
X-thorax 2 directions	0.216	8.03	0.157	7.08	0.184	6.91
EBUS	0.166	10.7	0.271	14.46	0.232	11.95
CT of the brain and/or skull	0.119	7.14	x	x	0.087	4.77
CT thorax zmc	0.085	4.23	0.071	3.38	0.077	3.28
WIG resectie	x	x	0.065	3.38	x	x
EUS	x	x	x	x	x	x
MRI brain with contrast	x	x	x	x	x	x
Echo heart and thorax	x	x	x	x	x	x
MRI scan	x	x	x	x	x	x
Pleura punction diagnostic	x	x	x	x	x	x

Figure A.1: *Frequency Comparison Stage 0-2, Stratified by Period*

	Group A, stage 3 (6864 patients)		Group B, stage 3 (174 patients)		Group C, stage 3 (2300 patients)	
	Frequency rate	Prevalence	Frequency rate	Prevalence	Frequency rate	Prevalence
X-thorax incl. fluorescence	2.054	72.58	1.339	52.30	1.301	46.96
CT-thorax heart and great vessels	1.123	68.52	0.828	41.38	0.854	44.17
PET whole body	0.534	43.24	0.213	14.37	0.227	16.3
CT before PET/SPECT	0.376	30.84	0.149	10.92	0.173	12.04
Heart - echocardiography	0.188	11.01	0.098	4.60	0.118	6.26
Bronchoscopie	0.437	24.42	0.471	25.86	0.587	28.43
X-thorax 2 directions	0.157	x	x	3.45	x	x
EBUS	0.573	30.06	0.851	37.93	0.774	34.43
CT of the brain and/or skull	0.132	8.52	x	x	0.093	5.3
CT thorax zmc	x	x	x	x	x	x
WIG resectie	x	x	x	x	x	x
EUS	0.123	6.8	0.132	7.47	0.122	5.87
MRI brain with contrast	x	6.26	x	x	x	x
Echo heart and thorax	x	x	0.092	5.75	0.086	5.04
MRI scan	x	x	0.069	x	x	x
Pleura punction diagnostic	x	x	x	x	x	x

Figure A.2: *Frequency Comparison Stage 3, Stratified by Period*

	Group A, stage 4 (16000 patients)		Group B, stage 4 (295 patients)		Group C, stage 4 (5978 patients)	
	Frequency rate	Prevalence	Frequency rate	Prevalence	Incidence Rate	Prevalence
X-thorax incl. fluorescence	1.898	69.84	1.403	49.49	1.392	53.25
CT-thorax heart and great vessels	1.150	67.53	0.949	48.47	1.109	57.29
PET whole body	0.373	28.34	0.241	16.61	0.219	15.02
CT before PET/SPECT	0.271	21.02	0.183	13.22	0.173	12.06
Heart - echocardiography	0.174	9.78	x	x	0.125	x
Bronchoscopie	0.303	16.65	0.464	23.05	0.363	18.07
X-thorax 2 directions	0.142	x	x	x	x	x
EBUS	0.204	10.86	0.403	19.66	0.309	14.55
CT of the brain and/or skull	0.269	14.80	0.247	13.90	0.291	15.52
CT thorax zmc	x	x	x	x	x	x
WIG resectie	x	x	x	x	x	x
EUS	x	x	0.108	x	x	x
MRI brain with contrast	x	7.36	0.129	8.81	x	8.41
Echo heart and thorax	x	x	x	6.44	0.131	7.85
MRI scan	x	x	x	x	x	x
Pleura punction diagnostic	0.145	8.62	0.122	6.44	0.148	8.16

Figure A.3: *Frequency Comparison Stage 4, Stratified by Period*

A.2 Three Most Common Pathways

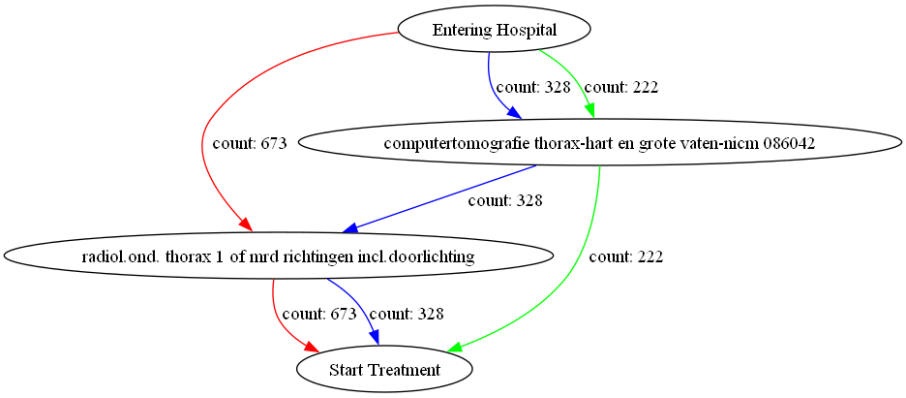

Figure A.4: *Three Most Common Pathways for Group A, Stage 0-2*

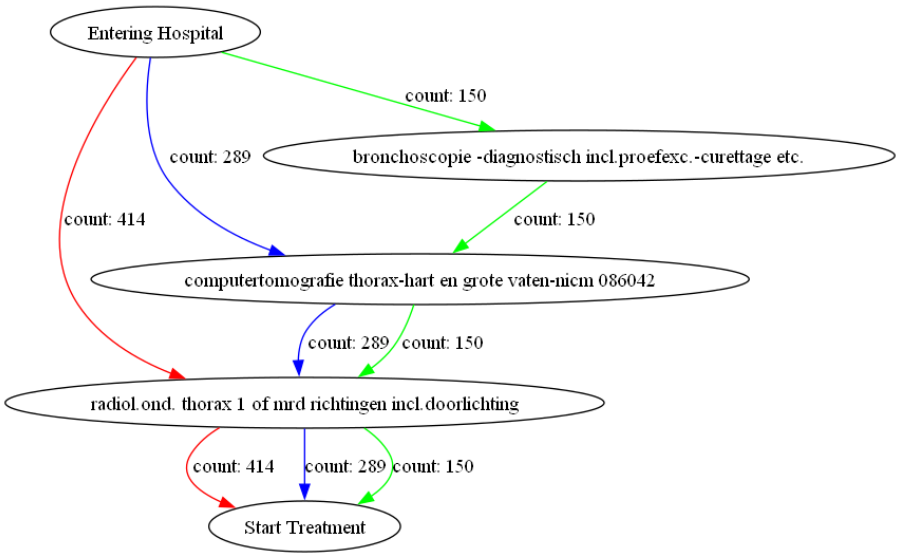

Figure A.5: *Three Most Common Pathways for Group A, Stage 3*

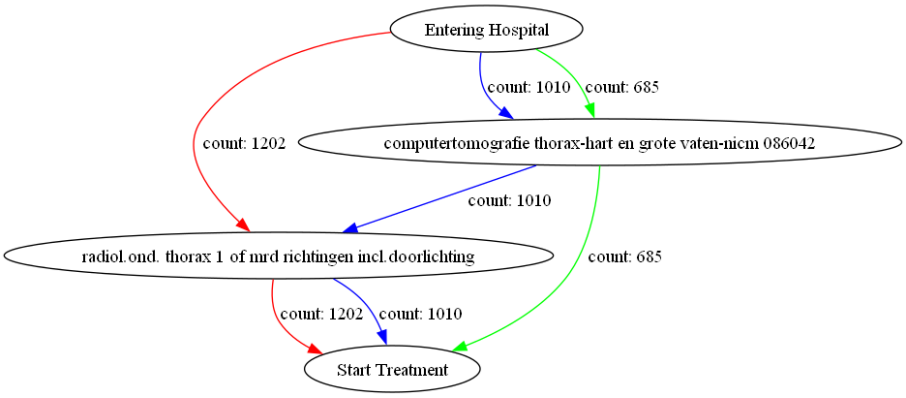

Figure A.6: *Three Most Common Pathways for Group A, Stage 4*

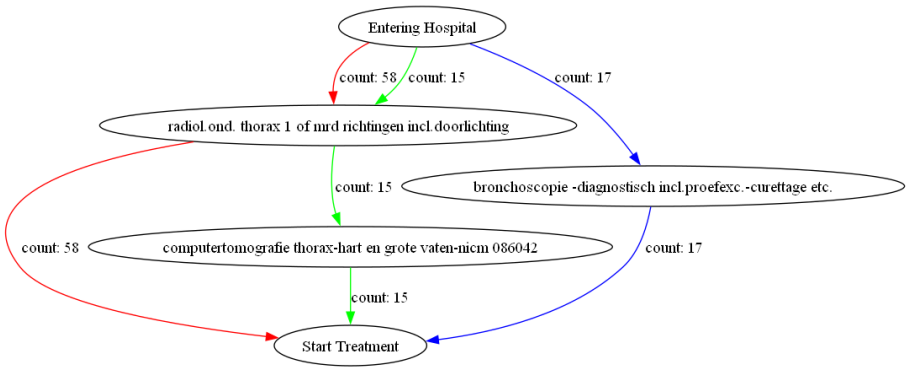

Figure A.7: *Three Most Common Pathways for Group B, Stage 0-2*

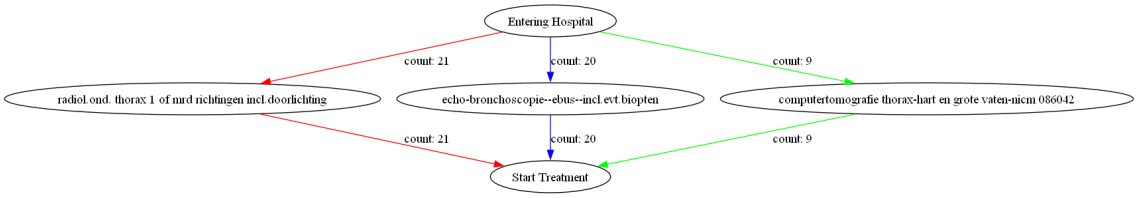

Figure A.8: *Three Most Common Pathways for Group B, Stage 3*

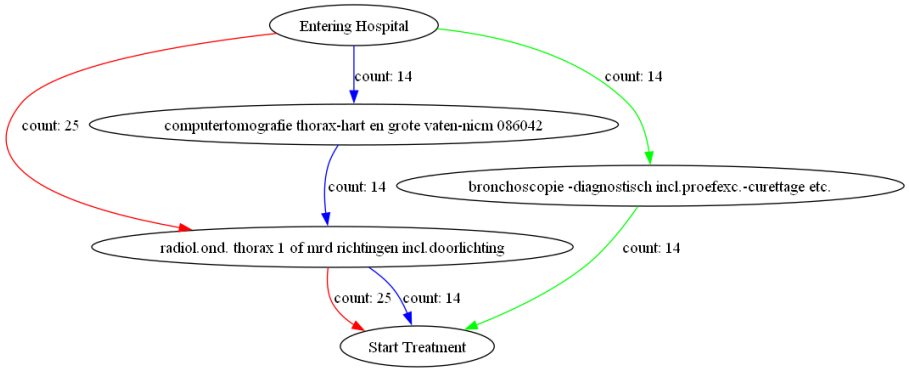

Figure A.9: *Three Most Common Pathways for Group B, Stage 4*

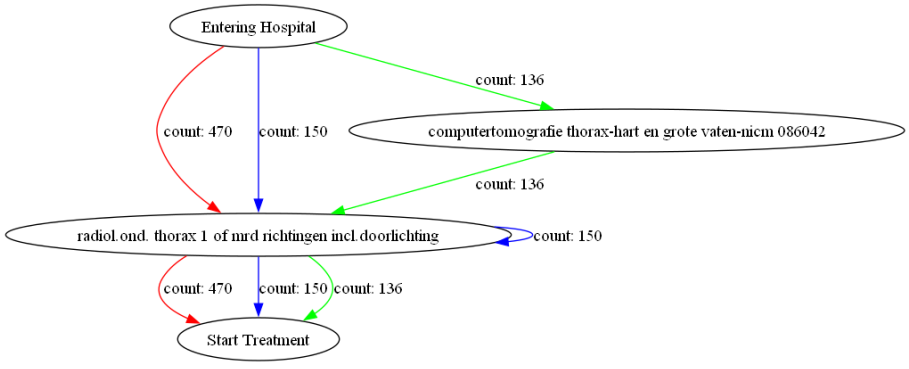

Figure A.10: *Three Most Common Pathways for Group C, Stage 0-2*

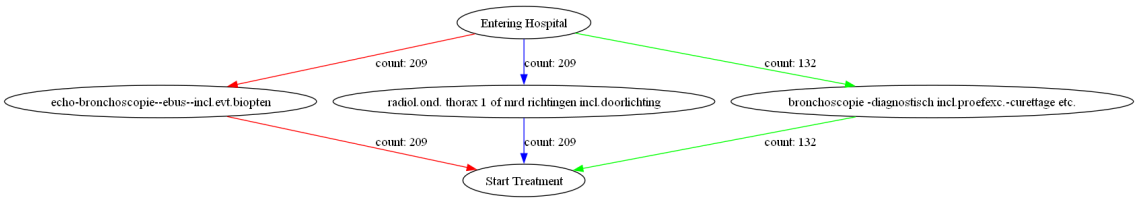

Figure A.11: *Three Most Common Pathways for Group C, Stage 3*

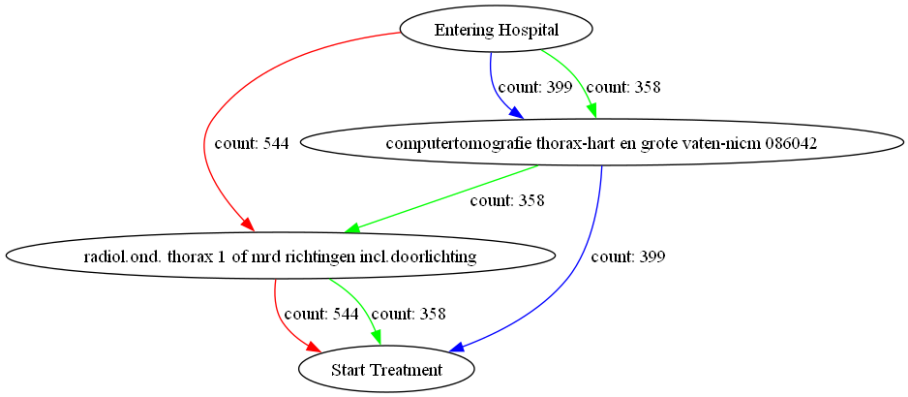

Figure A.12: *Three Most Common Pathways for Group C, Stage 4*

A.3 Heuristic Nets

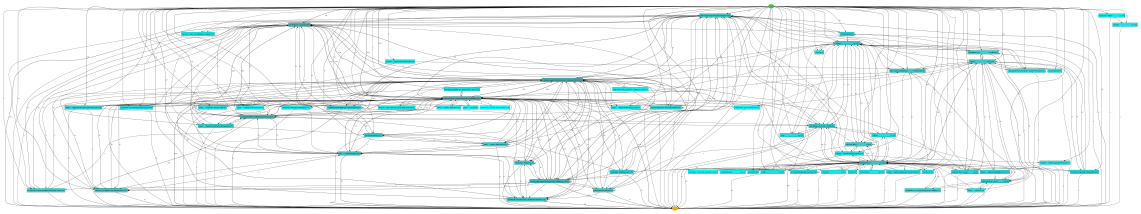

Figure A.13: *Heuristic Net for Group A, Stage 0-2*

A.4 Heuristic Nets for 10 Most Frequent Activities (A and C)

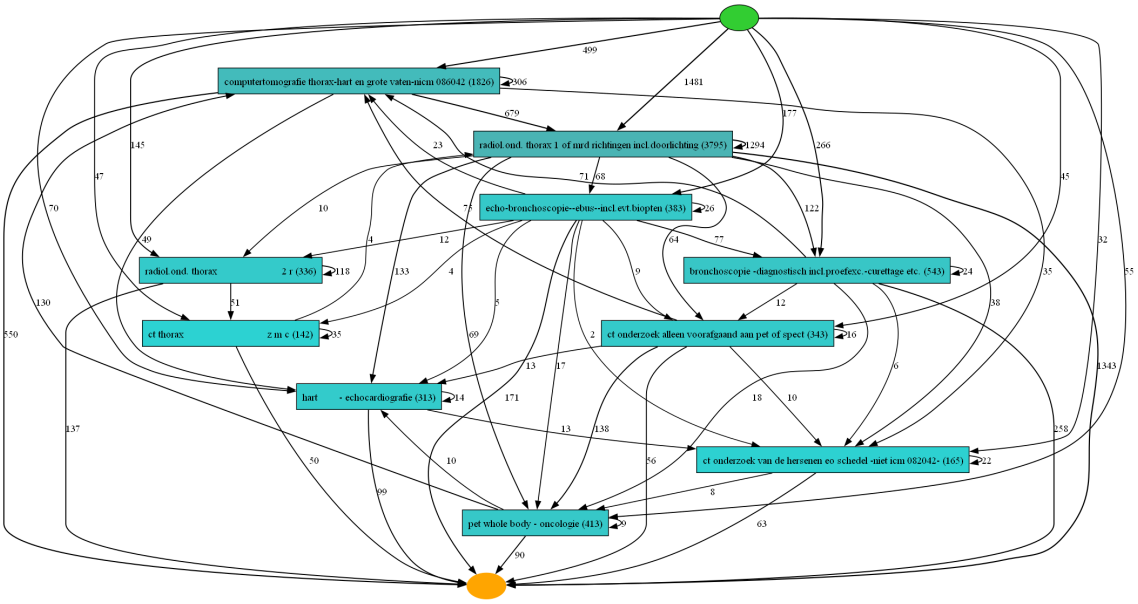

Figure A.14: *Heuristic Net for 10 Most Frequent Activities for Covid Group C, Stage 0-2*

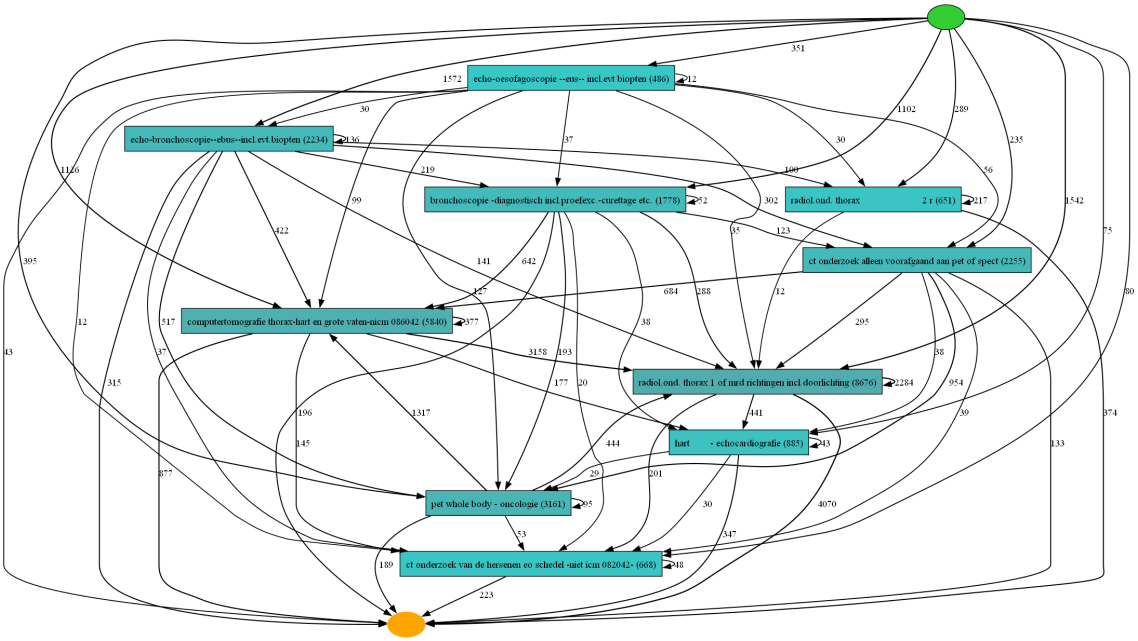

Figure A.15: *Heuristic Net for 10 Most Frequent Activities for Covid Group A, Stage 3*

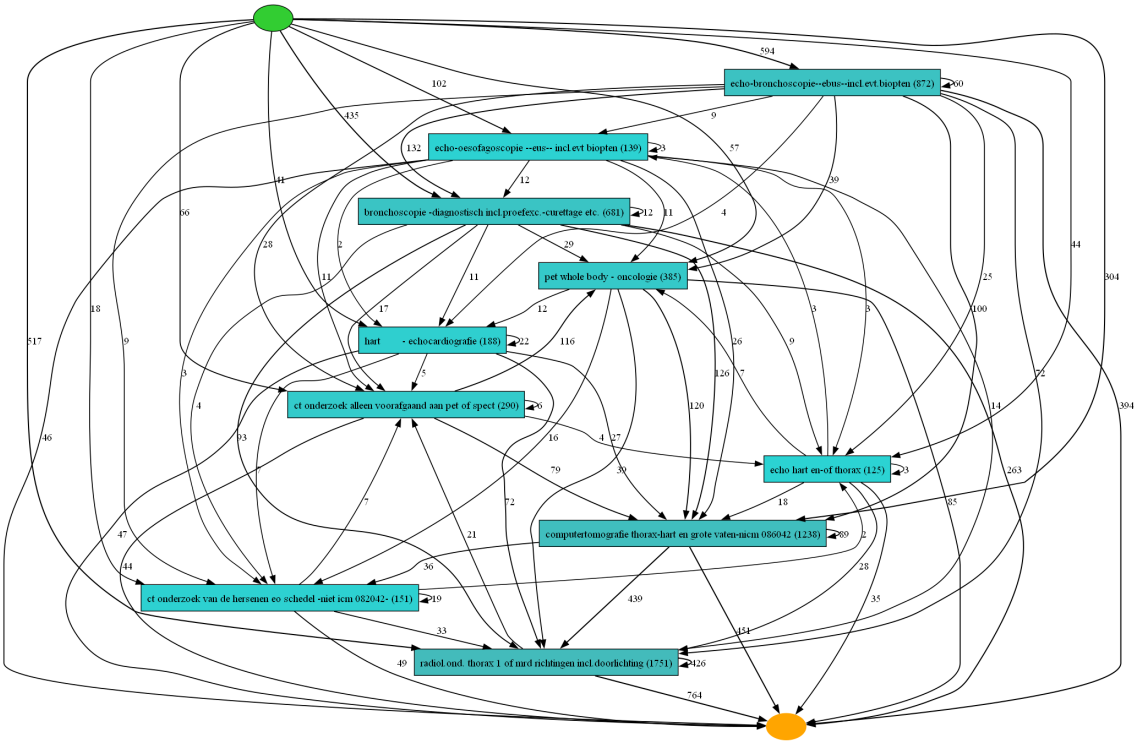

Figure A.16: *Heuristic Net for 10 Most Frequent Activities for Covid Group C, Stage 3*

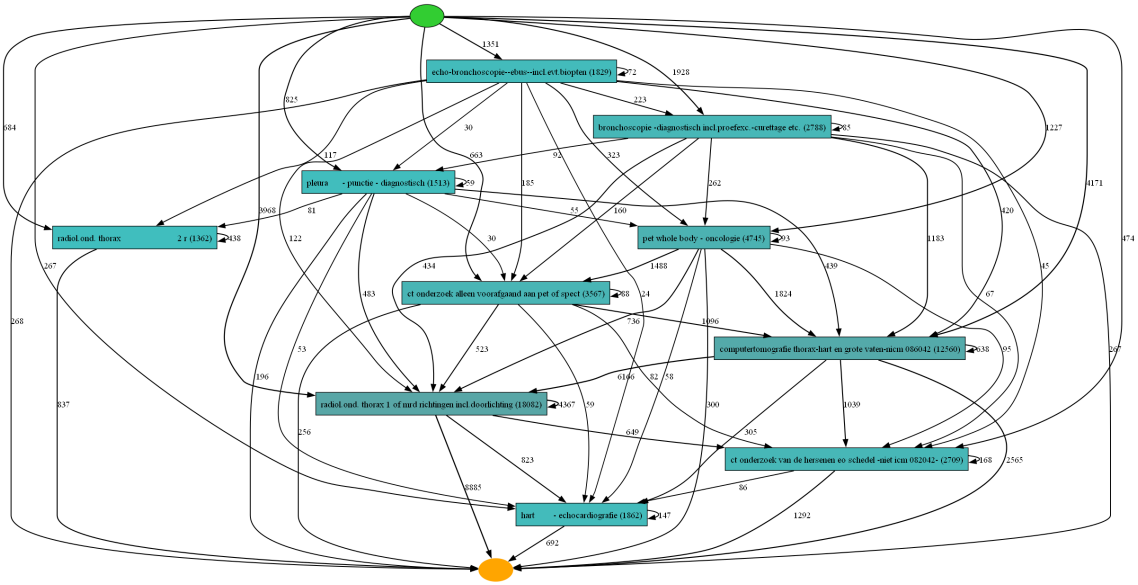

Figure A.17: *Heuristic Net for 10 Most Frequent Activities for Covid Group A, Stage 4*

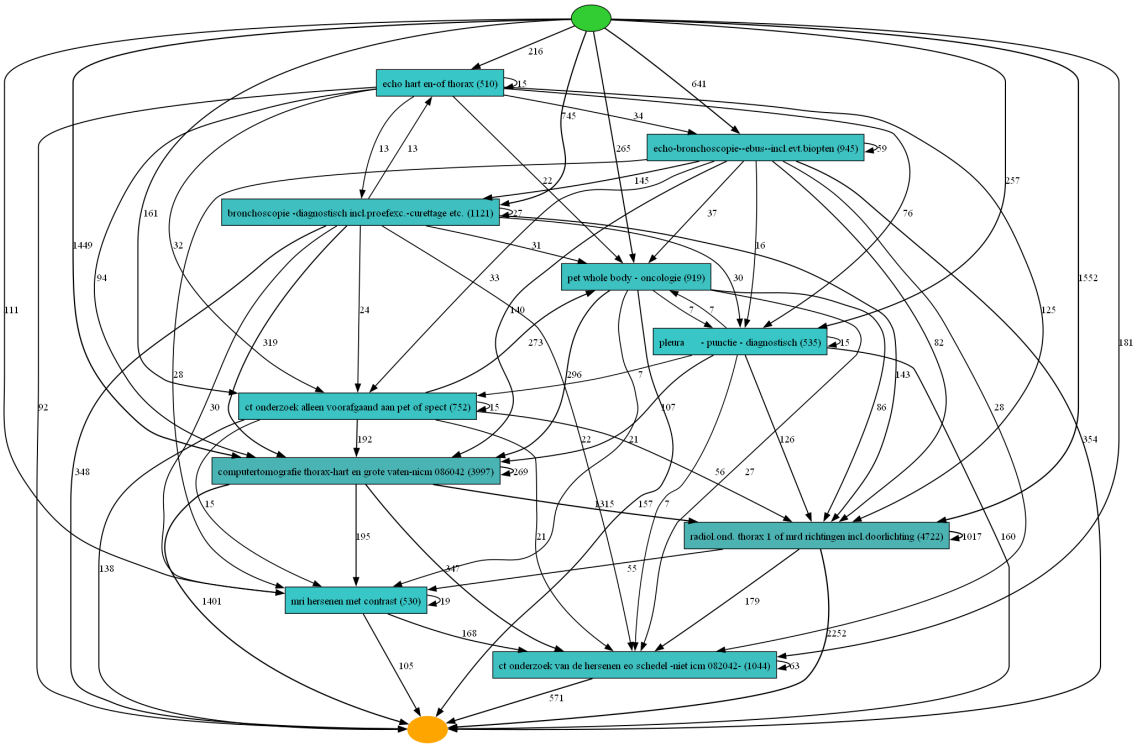

Figure A.18: *Heuristic Net for 10 Most Frequent Activities for Covid Group C, Stage 4*

A.5 Heuristic Nets for Aggregated Activities (A and C)

Group	**Diagnostic Activities**
Biopsy	ct-gel. als ass. bij punctie - biopsie thorax, echogeleide als ass. bij punctie-biopsie hals-schildklier, diagn.punctie-biops.niet palp.afw.-organen -echocontrole, pleura - biopsie, echogeleide als ass. bij punctie - biopsie pleura, bronchus - biopsie via scopie, longen - longbiopsie dmv endoscopie, echogeleide als ass. bij punctie - biopsie thorax, echogeleide als ass. bij punctie - biopsie long, longen - percutane naaldbiopsie long, diagn.punctie-biops.niet palp.afw.-organen mri-controle, longen - biopsie - open, pleura - biopsie als zelfst.ingreep dmv steelboor, mediastinum - biopsie dmv mediastinoscopie, echogeleide als ass. bij punctie - biopsie long - rechts, echogeleide als ass. bij punctie - biopsie pleura- rechts, pleura - biopsie via thoracoscopie, mediastinum - biopsie, pleura - biopsie als zelfstandige ingreep, longen - longbiopsie dmv thoracoscopie, bronchus - diagn.starre tracheobronchoscop.met biopsie

Group	Diagnostic Activities
Bronchoscopy	bronchoscopie -diagnostisch incl.proefexc.-curettage etc., echo-bronchoscopie–ebus–incl.evt.biopten, bronchus - flexibele bronchoscopie nno, bronchus -ther.scopie-verw.corp.al.-afzuig.-instal.med, bronchus - diagnostische bronchoscopie, bronchus - bronchoscopie met brush en spoelen, longen - perifeer longbiopt mbv bronchoscopie, bronchus - bronchoscopie met echo-probe, bronchus - bronchoscopie met elektrocoagulatie, bronchus - starre therapeutische bronchoscopie, bronchus - ther.scopie-lasercoagulatie-stentplaatsing, bronchus - bronchoscopie diagnostisch -starre scoop-, bronchus - bronchoscopie met lavage, bronchus - scopie diagnostisch mbv fiberscoop, longen - transbronchoscop.needle aspiration –tbna–, bronchus - bronchoscopie -star- met carinapunctie, bronchus - therapeutische bronchoscopie mbv laser, bronchus - bronchoscopie met plaatsen stent, longen - broncheo-alveolaire lavage - bal, bronchus - scopie by kind.jonger dan 1 jr - fiberscoop, longen - diagnostische bronchoscopie met chartismeting, bronchus - bronchoscopie met cryocoagulatie, bronchus - bronchoscopie met argonplasmacoagulatie
Cardio	hart - echocardiografie, pet partieel –neurologisch-cardiologisch–, pet-ct-scan myocardperf.in rust -volum.ejectfr.-flowmet.
CT lower extr	ct onderzoek onderste extremiteit mz intraveneus contrast
CT Neuro	ct onderzoek van de hersenen eo schedel -niet icm 082042-, ct schedel z c, ct hersenen z c, ct hersenen m c, ct arterien hersenen m c, ct schedel z m c, ct schedel m c, ct schedel - perrfusie m c
CT Thorax	computertomografie thorax-hart en grote vaten-nicm 086042, ct onderzoek alleen voorafgaand aan pet of spect, ct thorax z m c, ct thorax m c, computertomografie luchtwegen - niet icm 085042, ct - gr.opl.vermogen-rapid seq. thorax, ct long z c, ct hersenen z m c, ct carotiden m c, ct thorax z c, ct arterien thorax m c, ct-gel. als ass. bij drainage thorax
CT upper extr	ct hals z m c, ct circle willis m c, ct hals z c, ct schedelbasis-sfenoid-sella z c
EBUS	bronchus - endobronchiale echografie –ebus–
Echo Thorax	echo hart en-of thorax, echo thorax, echo pleura, echo long, echo-oesofagoscopie –eus– incl.evt biopten
EUS	echo-oesofagoscopie –eus– incl.evt biopten
Mediastinoscopy	mediastinum - mediastinoscopie, mediastinum - excisie aandoening dmv mediastinoscopie, mediastinum - percutane mediastinumbiopsie, lymf.syst. - exc.mediastin.lymfekl.dmv mediastinoscopie, mediastinum - mediastinoscopie - anterior
Mediastinotomie	mediastinum - mediastinotomie

Group	Diagnostic Activities
MRI Neuro	mri hersenen met contrast, mri hersenen - standaard, mri achterste schedelgroeve -niet icm 081290- -max 2-, mri neuro m c, mri hersenen - uitgebreid, mri grote hersenen, mri hersenen - diffusie z c, mri schedel, mri neuro z c, mri hersenen - stereotactisch, mri hersenen - perfusie m c, mri aangezicht, functionele mri hersenen, mri midden hersenen-hypofyse-epifyse z m c, mri schedel m c
MRI Thorax	mri thorax –wand– en mediastinum excl.mamma, mri thorax z m c, mri thorax
MRI upper extr	mri aangezicht z m c, mri hals inclusief mra hals
Puncture	pleura - punctie - diagnostisch, pleura - punctie - therapeutisch, longen - diagnostische transthoracale longpunctie, pleura - diagnostische punctie onder echografie, longen - punctie, pleura - diagn. punctie of aspiratie pleuraholte, drainage abces onder echocontrole, pleura - punctie - ontlastend
SPECT	spect van de hersenen, spect van longperfusie, spect van thorax
Spect Thorax	spect van thorax
Thorascopie	thorax - thoracoscopie - diagnostisch
Whole body CT	ct totale lichaam, ct onderzoek bovenste extremiteit mz intraveneus contrast, ct total body scan exclusief preventief onderzoek
Whole body MRI	mri-scan, mri hals
Whole body PET Scan	pet whole body - oncologie, totale lichaam - pet ct-scan - 18f fdg, tumor - petscan totale lichaam 18-f desoxygl, totale lichaam - pet carvedilol, totale lichaam - pet ct-scan 68ga psma, totale lichaam - pet ct-scan ga-68 dotatate, totale lichaam - pet ct-scan ga-68 dotatoc, totale lichaam - pet ct-scan 18-f choline, totale lichaam - pet ct-scan - 18f dopa, totale lichaam pet-ct scan 18-f psma
WIG resectie	longen - wigresectie mbv video-ass.thor.surg.–vats-, longen - wigexcisie enkelzijdig mbv vats, longen - wigresectie - open procedure, longen - wigresectie dmv thoracoscopie, longen - wigexcisie, longen - bilaterale wigresectie - midsternaal, longen - wigexcisie dubbelzijdig
X-Thorax	radiol.ond. thorax 1 of mrd richtingen incl.doorlichting, radiol.ond. thorax 2 r, radiol.ond. doorlichting zonder opnamen thorax, radiol.ond. thorax 1 r, radiol.ond. thorax - op zaal 1 r, radiol.ond. thorax - in bed 1 r, thorax - beoordeling x-thorax voor derden, doorlichting zonder opname longen, doorlichting zonder opname hart en grote vaten, radiol.ond. hart en grote vaten 3 r

Table 4: *Aggregation of Diagnostic Activities [24]*

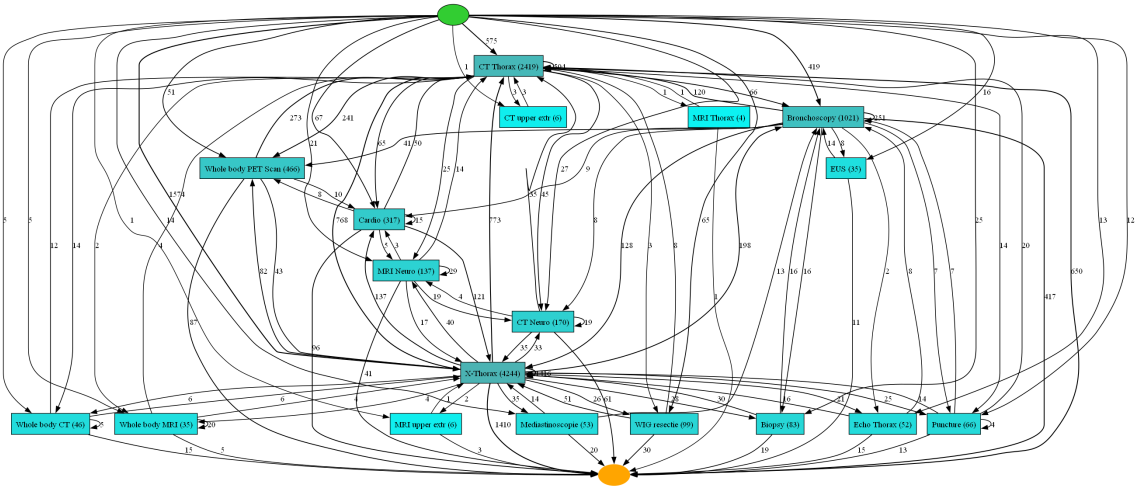

Figure A.19: *Heuristic Net with Aggregated Activities for Covid Group C, Stage 0-2*

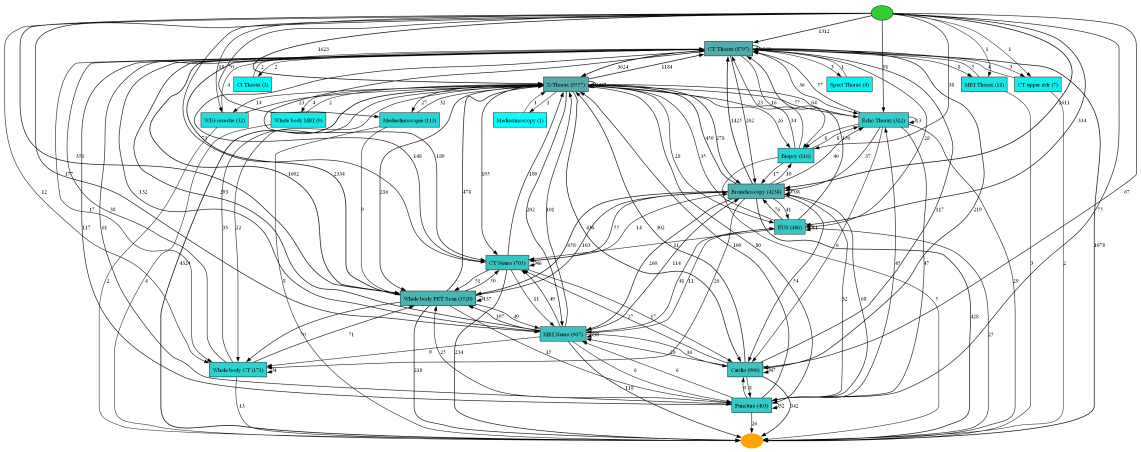

Figure A.20: *Heuristic Net with Aggregated Activities for Covid Group A, Stage 3*

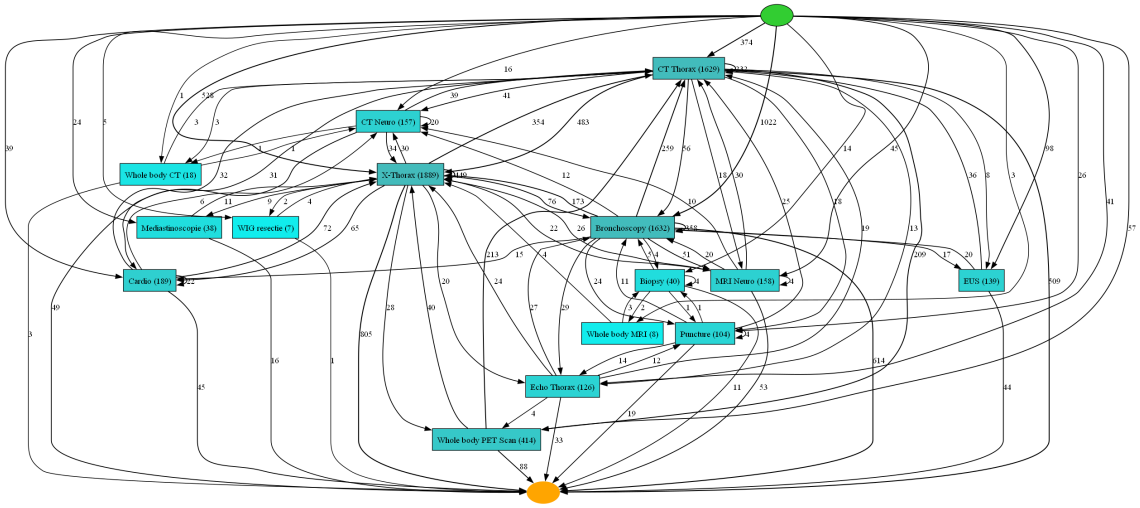

Figure A.21: *Heuristic Net with Aggregated Activities for Covid Group C, Stage 3*

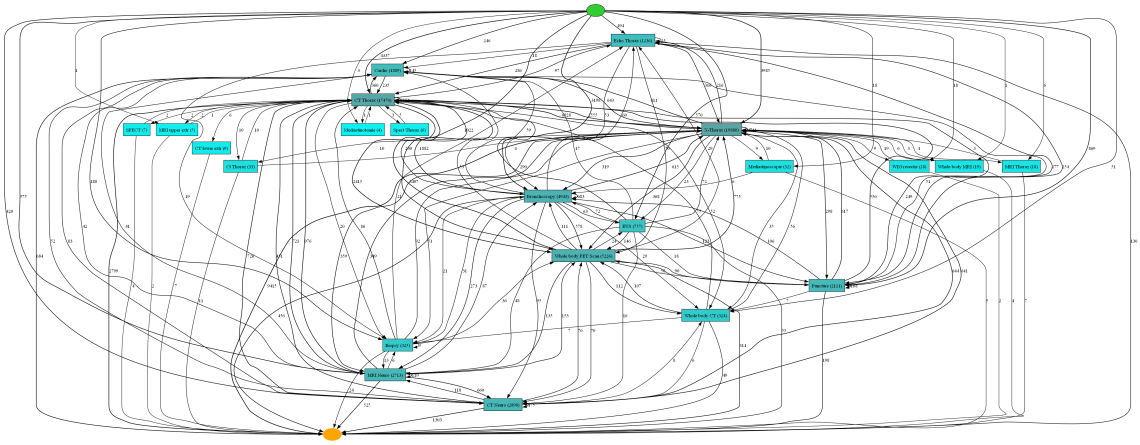

Figure A.22: *Heuristic Net with Aggregated Activities for Covid Group A, Stage 4*

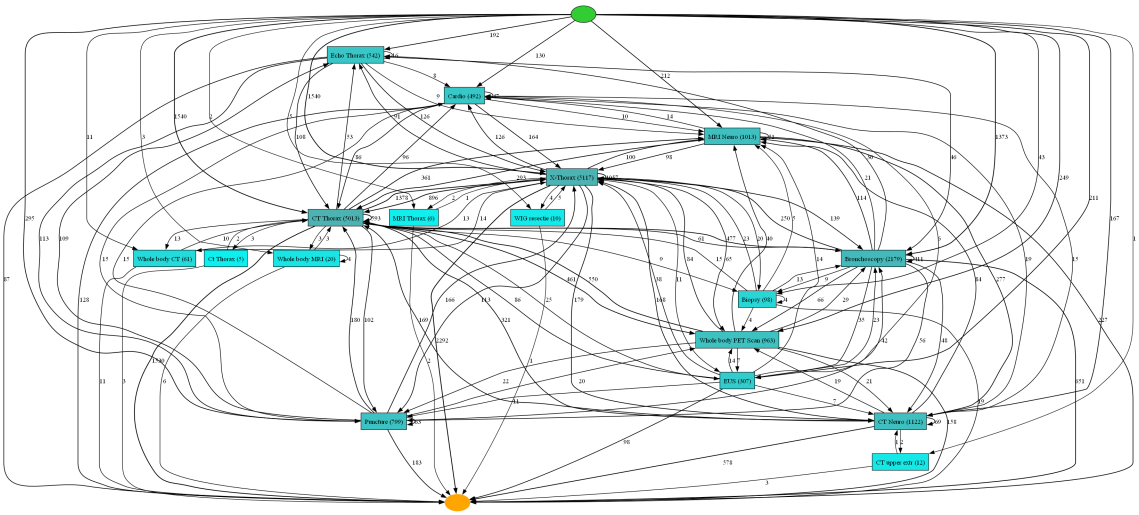

Figure A.23: *Heuristic Net with Aggregated Activities for Covid Group C, Stage 4*