**Mining Lethal Adverse Event Association Patterns in Clinical Trials Using Big Data Analysis**

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**Abstract**

**Background and aim:** Patient’s death is the most significant adverse event that could happen in a clinical trial. Currently there is a lack of study to analyze the critical clinical trial factors that associated with patient’s death. In this study, we aim at analyzing clinical trial factors that associated with patient’s death in clinical trials.   
**Methods and Data**: We propose a data-driven analysis that uses association mining to systematically extract important trial factors that could be associate with patient’s death during a clincial study. The source data were extracted from ClinicalTrials.gov. In total, we extracted 10,127 clinial trials that reported research outcomes. Among these trials, 1,901 trials (18.77%) and 2697 trial-arms reported death of patients, total 17,845 patients died and 144,894 were at risk in death events. We conducted association analysis on patient’s death with trials fators, including intervention, target disease conditions, and trial phases. We also used FP-tree association mining method to uncover significant serious adverse events that could associated with patient’s death in clinical trials. Finally, we built a multiclass classification model from strong associated features including Number of Participants, Participants Mean Age, trial Phase, target disease Conditions, Interventions and serious adverse events.

Results:

We extract each phase trials#, the percentage of death trials among them, the death incidence and each phase p-Value against the reference phase, so does the similar extraction to top 20 interventions and top 20 target disease conditions. We also generate top frequency and top confidence serious adverse events, meanwhile summarize the top 20 adverse event categories. Finally, we generated a comprehensive multiclass classification model with 2069 features, the purpose to do these summaries is going to get top influenced features to “Death”.   
Conclusion:

**Introduction**

(Clinical trial is a risky research) Clinical trials are often designed to test the efficacy and safety of new treatments. Clinical trials can only be conducted after they have received [ethics committee](https://en.wikipedia.org/wiki/Institutional_review_board)’s approval when the rights and welfare of participated human subjects can be protected. Due to the experimental nature, clinical trials inherently have a higher risk of serious adverse events. For example, in July 2016 two cancer treatment trials reported death, and one of trials were temporally halt by FDA for review. Understanding the risk of patient’s death in clinical has great value for clinical trial monitoring and planning. However, currently little study has been done to systematically analyze the death patterns in clinical trials. In this paper, we propose an exploratory study to analyze the risk patterns of patient’s death that associated with various clinical trial factors, including clinical trial phrases, targeted conditions, interventions, and other co-occurred serious adverse events in trials. This study applied association mining to analyzes the risk of potential factors that associated patient’s death in clinical trials.

(Why we use association rule mining? . [**in medical domain**] ) Association rule mining is an effective method to uncover correlation patterns from data set. In the healthcare domain, various studies have applied association rule mining method to discover meaning interesting knowledge.

(示范) For example, Brossette et al, (Brossette, Sprague et al. 1998) applied association mining method to the infection control dataset in the UAB Hospital laboratory information system. They uncovered 28-57 statistically significant events in the occurrence of infection or antimicrobial resistance of a bacterium. To discover multiple-item drug adverse event associations, Harpaz et al (Harpaz, Chase et al. 2010) proposed an association mining technique on the FDAs spontaneous adverse event report data. The results uncover new drug-drug interactions that were not reported or validated in previous studies.

In order to explore the labyrinthian network of ADHD comorbidity, Yueh-Ming Tai(Tai and Chiu 2009) has demonstrated the possibility to use Association Rule Mining in comorbidity studies. Their study has showed the higher risk in psychiatric comorbidity than other physical illnesses, and other benefits to apply association rule mining to ADHD comorbidity in large clinical databases.

S. Concaro(Concaro,2011) has gained better vision of health care activities by exploring large amount administrative health care data, they redesigned the temporal association rules to have hybrid events, which possess the heterogeneous temporal nature. They discovered the patterns of diabetic patients compared to the control group, meanwhile to check the compliance in clinical care flow with regional health care agencies.

Sharma, D(Sharma 2016) has targeted to find some strong associations between drugs and associated reactions from Adverse Event Reporting system. With Association Rule Mining, they discovered strong patterns of correlations between attributes from large data repositories, specifically having both micro and macro drug adverse reactions in the serious consequence.

We applied association analysis methods to rank clinical trial factors based on the observance of death of patients.

**Methods**

# Which algorithm we chose, how to understand the algorithm?

In our research, we used FP-Growth as step 1 to mine serious adverse events, and then use Associations Rules as step 2 to generate rules to discover internal adverse events patterns. The apparent advantage of FP-tree algorithm, that it allows frequent itemsets discovery without candidate itemsets generation, which is faster than Apriori. In FP-Growth, there are only 2 passes over data set. In first pass, the algorithm will scan data and find support of each item, then prune infrequent items if its support is below minimum threshold. After that, the algorithm builds a compact FP-tree structure by adding instances of frequent items in non-increasing order based on their support, so common prefixes can be shared. FP-tree will compress data if many instances added to FP-tree share most frequent items, thus FP-tree provides higher compression close to the tree root. In second pass, the FP-growth reads one transaction at a time and maps it to a path, paths can overlap when transactions share prefix items. The more paths have overlap, the higher the compression. Finally extract frequent itemsets from the FP-tree. In step 2, we are only interested to the consequent Y to be “death”, we want to know what are top adverse events, which contribute higher confidence to death, and what are the pattern changes impacts to confidence of death(Zhihui Luo 2013). Death incident in clinical trial is not trivial and even severe controversial ethical issue, knowing the association rules of adverse events with death can help healthcare professionals to plan better clinical trial treatment.

(**move to method section**) One significant constraint of association rules is filtering an antecedent by a consequent, (antecedent is also called left-hand-side (LHS), and consequent right-hand-side (RHS)). Suppose, given a set of transactions T on database, a set of n items called I, each T has a subset of items from I. An antecedent is a union of any size of item set X found in some T, a consequent is an item Y found from having antecedent transactions. We identify Support (X) is an indication of how frequent or proportion an event item appeared in the transactions, while the Confidence (X=>Y) indicates the number of times when if X occurs then Y follows statements are true, which means the proportion of transactions to have both item sets of X and Y in all X-transactions (X∩Y= Ø, and X, Y⊆ I).

# Getting serious adverse event frequency

In our study, we downloaded 201,710 clinical trials published on ClinicalTrials.gov till Dec 1, 2014, and stored them in a local non-SQL database. About 5% of trials have recorded “Study Results”, 99.8% of them has recorded both Serious and Other Adverse Events table , each table was composed of at least one experimental arm, and each arm recorded at least one adverse event during clinical trial process. We found “death” adverse event is very frequent appeared in Serious Adverse Event arms, so data mining “death” adverse event from Serious Adverse Event arms became our focus. For naming convention, we call an arm is risky when some adverse events in that arm have participants affected / at risk is bigger than “0”. Finally, we extracted 20,943 risky serious adverse event arms from entire database. These arms reported at least one serious adverse event, which has at least one affected patient. We discovered there are 2,591 death incidents occurred among the 20,943 Serious Adverse Events arms, on average there is a probability of observing 1 death incident among 8 serious risk arms, this is an alarming reflection - serious adverse events are telling “stories”. The “stories” unfolds the side-effect relationship among adverse events, the new questions will be - what is other serious adverse event that appears in high frequency when death occurs in clinical trials, and what are serious adverse events with higher confidence to death in an apparent manner.

# We also review other vital factors of clinical phases, conditions and interventions from observed serious adverse event trials. Knowing these factors can help to understand clinical research treatment plan or protocol in specific stages, we compare the significance difference between non-death observed trials and death-observed trials, to discover subgroup of phases, conditions and interventions terms which have strong correlation to Death serious adverse events. Specific to serious adverse events, using machine learning algorithm FP-Growth, we extracted high frequency single serious adverse events with minSupport 0.00815, and we picked the top 100 single events to review further. Meanwhile, we take top 100 single, and top 100 pair/triple serious adverse events according to descending confidence to death with minConfidence 0.4. A further exploration has been achieved by showing high frequent single serious adverse event may not be proportional to high confidence to death. We also discover a list of top events, which increase the confidence to death tremendously from a single adverse event to a double, or triple event set.

# Consider the study results are from a big geography coverage and great diversity of recruited patients, hence studying them are solid references to make assumption on future clinical trial planning. In order to dig out further, we will summarize and compare the patterns from different perspective in later sections.

# Results:

This is a table to compare intervention and conditions from “Death” serious adverse events arm to all serious adverse events arms, in order to observe what are the most frequent interventions and conditions in clinical trials are strong associated with “Death”. For all intervention and conditions details, please refer to Appendix 1-2.

Clinical trials are conducted in a series of studies, which normally called trial phrases. Table 1 summarize the average death incidence rate and prevalence from phase type perspective. We can see phase 2, phase 3 or their combination have most prominent prevalence in death adverse events, both phase 2 and phase 3 involves more than 3,000 clinical trials, with >600 clinical trials observed death from Serious Adverse Events. During these 2 phases, the drug or treatment is given to a large group of patients to test its effectiveness, monitor side effects, evaluate its safety, and compare it to commonly used groups, thus lethal adverse events will be more frequent to observe. However, phase 1 has the largest average death incidence to 11.81%, because researchers test a new drug or treatment to a small group of people for the first time to evaluate its effectiveness, safety, dosage range, and identify its side effects, the risk to cause death would be high after studies are done in latter phases. Phase1/Phase2 and Phase 2 itself have higher P-value compare to Phase 1(reference), it’s apparent to see Phase 2 has broad evaluation scope, which could have unusual extreme changes compare to Phase 1, some may not be relevance to clinical study.

Table 1: Phrases of trials and their association with death (Death from serious adverse events)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Phase Type | #Total Trial | #Trials Observed Death | % of the Trial Observed Death | Average Incidence rate(Death)  Average of Affected/At\_risk  (arms#) | P-value |
| Phase 1 | 382 | 35 | 9.2% | 11.81% | Reference group |
| Phase 1/ Phase 2 | 414 | 80 | 19.32% | 8.65% | P=0.0891 (P<0.1) |
| Phase 2 | 3346 | 616 | 18.41% | 8.55% | P=0.0659 (P<0.1) |
| Phase 2/ Phase 3 | 181 | 42 | 23.20% | 2.36% | P=2.4223E-05 (P<0.0001) |
| Phase 3 | 3716 | 746 | 20.08% | 1.30% | 4.0918E-06 (P<0.0001) |
| Phase 4 | 1244 | 183 | 14.71% | 2.0% | 1.2610E-05 (P<0.0001) |
| Trials did not reported Phase(NA) | 837 | 173 | 20.67% | 3.97% | 0.000322731 (P<0.0001) |

We collected total 10027 unique interventions and 4554 unique conditions from clinical trials which have serious adverse events arms. Specifically, 2263 unique interventions and 1525 unique conditions are observed from clinical trials which have “Death” in their serious adverse events arms. Table 2 groups clinical trials based on their target conditions. The average incidence and prevalence in trials of patient’s death in each of the trial groups were summarized.

The top 20 conditions in terms of death prevalence are anaplastic\_astrocytoma, which is a rare malignant brain tumor at 83.33%, recurrent\_uterine\_sarcoma is recurrent uterine cancers, such cancers are malignant and rare, representing at 71.43%, ischemic\_stroke and recurrent\_small\_cell\_lung\_cancer are at 60.00%. However, from average incidence, the top 3 are multiple\_myeloma\_and\_plasma\_cell\_neoplasm at 43.74%, myelodysplastic\_syndromes at 32.02%, lymphoma at 27.93%, trials with these 3 conditions have higher percentage of patients are affected to Death.

Table 2: Top trial targeted disease conditions that associated with patient’s death (based on serious adverse event)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Condition** | **All Trials(#)** | **Death Trials(#)** | **Death Trials/All Trials** | **Average Incidence** |
| multiple\_myeloma\_and\_plasma\_cell\_neoplasm | 24 | 7 | 29.17% | 43.74% |
| myelodysplastic\_syndromes | 48 | 13 | 27.08% | 32.02% |
| Lymphoma | 91 | 26 | 28.57% | 27.93% |
| recurrent\_colon\_cancer | 13 | 5 | 38.46% | 20.21% |
| recurrent\_rectal\_cancer | 13 | 5 | 38.46% | 20.21% |
| acute\_lymphoblastic\_leukemia | 16 | 6 | 37.50% | 19.53% |
| Leukemia | 106 | 45 | 42.45% | 19.36% |
| Myelofibrosis | 12 | 5 | 41.67% | 17.98% |
| non-hodgkin's\_lymphoma | 36 | 9 | 25.00% | 16.21% |
| recurrent\_uterine\_sarcoma | 7 | 5 | 71.43% | 13.92% |
| stage\_iv\_breast\_cancer | 27 | 7 | 25.93% | 13.66% |
| acute\_myelogenous\_leukemia | 24 | 10 | 41.67% | 12.09% |
| myelodysplastic\_syndrome | 39 | 20 | 51.28% | 11.75% |
| ischemic\_stroke | 15 | 9 | 60.00% | 10.62% |
| kidney\_cancer | 19 | 5 | 26.32% | 10.31% |
| anaplastic\_astrocytoma | 6 | 5 | 83.33% | 10.25% |
| ovarian\_cancer | 73 | 9 | 12.33% | 9.72% |
| stage\_iv\_pancreatic\_cancer | 13 | 6 | 46.15% | 9.55% |
| recurrent\_small\_cell\_lung\_cancer | 10 | 6 | 60.00% | 9.42% |
| chronic\_lymphocytic\_leukemia | 21 | 5 | 23.81% | 8.88% |

In Table 3, we show the top 20 clinical trial interventions that associated with patient’s death. The rows are sorted by the count of trials >=5 (column 2). The most common type of intervention is the placebo group. Placebo is often served as a control in clinical trials, thus it is the most common intervention type. Among 2286 trials arms that used placebo intervention, 368 (16%) of trial arms observed patient’s death. The average death incidence rate of the placebo intervention is 1.66%. We used the placebo group as a baseline reference group to compare the statistical significant of other interventions. Among the top 20 interventions, XX (XX%) of the interventions are chemotherapies, such as XXXX with an average incidence rate of XXX (P-value<XXX), YYY with an XXX incidence rate, and ZZZ with an ZZZ incidence rate. XXX is the only antibody among the top 20. XXX is an antidiabetic drug…...

Table 3: High frequency interventions that associated with patient’s Death (based on serious adverse events)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Intervention** | **All Trials(#)** | **Death Trials(#)** | **Death Trials/All Trials** | **Average Incidence** | **P-Value** | Intervention Type |
| Placebo | 2286 | 368 | 16% | 1.66% | reference | Control |
| Filgrastim | 44 | 10 | 23% | 47.74% | 0.001538183 |  |
| Cyclosporine | 26 | 7 | 27% | 44.90% | 0.003247528 |  |
| Busulfan | 17 | 7 | 41% | 34.51% | 0.06522688 |  |
| mycophenolate\_mofetil | 31 | 7 | 23% | 31.52% | 0.001788197 |  |
| stem\_cell\_infusion | 7 | 5 | 71% | 30.65% | 0.056949866 |  |
| Tacrolimus | 51 | 13 | 25% | 25.50% | 0.002353929 |  |
| imatinib\_mesylate | 34 | 12 | 35% | 22.70% | 0.005551617 |  |
| Saracatinib | 13 | 5 | 38% | 22.37% | 0.064126511 |  |
| Methotrexate | 102 | 25 | 25% | 22.36% | 0.00109703 |  |
| Vincristine | 30 | 8 | 27% | 21.90% | 0.048840666 |  |
| Melphalan | 40 | 16 | 40% | 20.55% | 0.012356535 |  |
| fludarabine\_phosphate | 34 | 10 | 29% | 17.94% | 0.187988588 |  |
| Fludarabine | 44 | 14 | 32% | 17.85% | 0.018730598 |  |
| Decitabine | 20 | 8 | 40% | 16.65% | 0.009033677 |  |
| Doxorubicin | 43 | 7 | 16% | 15.71% | 0.160282838 |  |
| cyclophosphamide | 161 | 43 | 27% | 15.57% | 0.002576175 |  |
| Etoposide | 66 | 22 | 33% | 14.92% | 0.043010921 |  |
| g-csf | 9 | 5 | 56% | 14.44% | 0.131780842 |  |
| polymorphism\_analysis | 8 | 6 | 75% | 14.41% | 0.027284506 |  |
| radiation\_therapy | 102 | 28 | 27% | 13.99% | 0.013599223 |  |

**Top 20 Single Frequent Events from Serious Adverse Events**

In table-4 shows the top 20 single frequent serious adverse events from 20943 serious risk arms. The complete list of top single serious adverse events is shown in Appendix-3. The table also displays the MedDRA categories (Brown, Wood et al. 1999) of the event, which indicate the affected body system. There are a total of 18 categories of adverse events were recorded in Table -4. We summarized single adverse event from both serious adverse event and other adverse event, and picked prominent serious adverse event to investigate further.

(See Table-4) the top frequent adverse event is “**Pneumonia**” - Infections and infestations, it has appeared in 4765 serious adverse events arms, compare to 1442 other adverse events arms. Among all serious adverse events arms, only 22.54% of arms have observed death. This reflects the fact, Pneumonia is a prevalent chronic condition, which has no strong association with “death” in a short time, but researchers reported Pneumonia has higher mortality among senior male hospitalized patients ages 65 and older than both sexes who are between 54-65 from 1976-86(LaCroix, Lipson et al. 1989). Such patients have a history of congestive heart failure, stroke, cancer, diabetes, or a history of chronic obstructive pulmonary disease and among men who were current smokers. Hence, knowledge of patients’ health history, quality of life, age, and gender are critical to assess Pneumonia associated death in specific clinical arm.

The second event is **Dehydration** - Metabolism and nutrition disorders, which has appeared in 2832 serious adverse events arms, 60.38% of all serious/other adverse events arms. It’s less frequent occurred than Pneumonia, however, 31.14% of serious adverse arms with Dehydration observed “death”, which means during all clinical trials, once it has Dehydration in serious adverse event, it’s very likely to have death adverse event from the same arm. In clinical practice, both water loss dehydration and salt and water loss dehydration endanger human life when water loss with or without salt at a rate faster than the body could replace them(Thomas, Cote et al. 2008). There is argument of accusing dehydration is a sign of poor care, like malnutrition or other associated with its development, which should bring clinical trials professionals’ focus to prevent dehydration in poor treatment, and find whether combination of physiological and disease is the culprit to bring it up.

The third adverse event is **Vomiting** - Gastrointestinal disorders, which has appeared in 2645 serious adverse events arms, and 30.59% of such arms have observed “Death”. Compare to 8547 other adverse events arms, it concludes v Among 2645 serious adverse event arms, there are 1673 arms have [Nausea,Vomiting], 1509 arms of [Vomiting Dehydration], and 1430 arms of [Vomiting Pneumonia]. It implies Nausea, Dehydration and Pneumonia could be possible serious conditions Vomiting associated with, less frequent vomiting is a recover sign from Dehydration. Treatment of these three serious conditions could monitor if vomiting is less frequent as outcome.

Another interesting event is **Sepsis** - Infections and infestations, which has high percentage to have death in its serious adverse events arms from top 20 frequent adverse events, 34.59% in 2099 arms. Furthermore, serious adverse events took 90.43% of all serious/other adverse events arms, informed that Sepsis is a risky adverse event. If sepsis progresses to sepsis shock, blood pressure drops dramatically, a very possible cause lead to death. Earlier treatment involved with appropriate antimicrobial and large amounts of intravenous fluids, is an important determinant of survival. A controlled study to examine the effect of inappropriate initial antimicrobial therapy on the prognosis of patients with sepsis showed 468 patients (52%) had documented bloodstream infection, and 211 patients (23%) received inappropriate initial antimicrobial therapy(Harbarth, Garbino et al. 2003). After they studied the 28-day mortality between adequately treated groups versus patients receiving inappropriate initial antimicrobial therapy, the report claimed inappropriate antimicrobial therapy was independently associated with increased mortality, hence appropriate early sepsis treatment is highly demanded.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Rank** | **Single adverse event** | **Event Organ Class** | **Serious Adverse Event Frequency (arms#)** | **Other Adverse Events Frequency (arms#)** | **% Occurred as Serious Event** | **Percentage of serious adverse events arms that observed death** |
| 1 | Pneumonia | Infections and infestations | 4765 | 1442 | 76.77% | 22.54% |
| 2 | Dehydration | Metabolism and nutrition disorders | 2832 | 1858 | 60.38% | 31.14% |
| 3 | Vomiting | Gastrointestinal disorders | 2645 | 8547 | 23.63% | 30.59% |
| 4 | Pyrexia | General disorders | 2387 | 5706 | 29.49% | 27.36% |
| 5 | Sepsis | Infections and infestations | 2099 | 222 | 90.43% | 34.59% |
| 6 | Nausea | Gastrointestinal disorders | 2096 | 11454 | 15.47% | 31.68% |
| 7 | Anaemia | Blood and lymphatic system disorders | 2080 | 3429 | 37.76% | 32.74% |
| 8 | Syncope | Nervous system disorders | 2036 | 701 | 74.39% | 31.93% |
| 9 | Cellulitis | Infections and infestations | 2012 | 686 | 74.57% | 28.93% |
| 10 | Abdominal\_pain | Gastrointestinal disorders | 1987 | 4189 | 32.17% | 29.29% |
| 11 | Dyspnoea | Respiratory, thoracic and mediastinal disorders | 1976 | 3378 | 36.91% | 33.45% |
| 12 | Atrial\_fibrillation | Cardiac disorders | 1901 | 541 | 77.85% | 32.61% |
| 13 | Gastroenteritis | Infections and infestations | 1891 | 1944 | 49.31% | 28.4% |
| 14 | Urinary\_tract\_infection | Infections and infestations | 1863 | 4193 | 30.76% | 31.83% |
| 15 | Myocardial\_infarction | Cardiac disorders | 1823 | 92 | 95.2% | 31.43% |
| 16 | Diarrhoea | Gastrointestinal disorders | 1754 | 8199 | 17.62% | 33.3% |
| 17 | Pulmonary\_embolism | Respiratory, thoracic and mediastinal disorders | 1731 | 149 | 92.07% | 33.1% |
| 18 | Chest\_pain | General disorders | 1730 | 1838 | 48.49% | 30.98% |
| 19 | Hypotension | Vascular disorders | 1643 | 2343 | 41.22% | 37.19% |
| 20 | Hypertension | Vascular disorders | 1600 | 5242 | 23.38% | 34.5% |

**Adverse Event Confidence to Death**

In table-5, we will review top confidence adverse events to Death, and the confidence change when group this event with other event together. This is the top 20-confidence single adverse event, which contributes to Death with pattern Antecedent -> Consequent (Death). As we discussed earlier, the Confidence (X=>Y) indicates the number of times when if X occurs then Y follows statements are true, the proportion of transactions to have both item sets of X and Y in all X-transactions.

Haematemesis is the vomiting of blood, a medical emergency in some cases is very severe and life threatening. It appears in total 352 arms, however a very high confidence of 0.5682 to “Death”. The top 3 adverse events associate with Haematemesis are Sepsis, Gastroenteritis and Syncope, with confidence range 0.7261- 0.7427, a dramatic mortality increase to Haematemesis. However, single serious adverse event Sepsis has confidence 0.34587899 to Death. If both Haematemesis and Sepsis appear in the same arms, the combination confidence to Death will increase to 0.7261, double of Sepsis’s confidence. This reflects Haematemesis as a single adverse event could endanger life much more than Sepsis does.

Skin ulcer can occur when an area of skin has broken down and exposed the tissue underneath it. Skin ulcer has confidence of 0.5352 to Death. The top 3 serious adverse events associate with Skin ulcer are Atrial\_fibrillation, Chest\_pain and Cerebrovascular\_accident, with confidence range 0.6955 - 0.7192.

Skin ulcer may follow with various cancers, the treatment of each type of cancer can include chemotherapy, radiotherapy, or surgery (that’s possible explanation for its high confidence to Death),

(Note: placebo, bevacizumab, and bi\_10773 are frequent interventions used in clinical trials which observed skin ulcer, possible interventions for cancers which will be followed by skin ulcer….)

The third high confidence single serious adverse event is Renal\_failure\_chronic, with confidence 0.5331 to Death. Chronic renal failure is commonly classified as a chronic kidney disease. The top 3 serious adverse events associate with Renal\_failure\_chronic are Cellulitis, Myocardial\_infarction and Cerebrovascular\_accident, with confidence range 0.6651 - 0.6822. kidney disease increases patients’ risk of having heart and blood vessel disease over a long period, heart disease is the major cause of death for all patients with chronic renal failure. Chronic kidney disease may be caused by diabetes, high blood pressure and other disorders. Early detection and treatment can often keep chronic kidney disease from getting worse.

(Note: placebo, peginesatide and ranibizumab are most frequent interventions used in clinical trials which observed Renal\_failure\_chronic serious adverse event…… )

After review Appendix -4, we could see Frequency and Confidence are two dimensions to evaluate an event’s frequency and weight. A good example of frequency-confidence comparison is between Haematemesis and Pneumonia. Haematemesis appeared in 352 arms, it has confidence of 0.5682 to Death. However, the top frequent adverse event Pneumonia has occurred 4765 times, but with only 0.2254 of confidence to Death. This informs one phenomenon, the more frequent adverse has a fewer contribution to Death.

Table 5: top 20 confidence single serious adverse events associated with death in clinical trials. (frequency <545)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Rank** | **Antecedent** | **Antecedent )** | **Organ Class** | **Frequency (arms#)** | **Other events associated with** | **Confidence Range** |
| 1 | Haematemesis | 0.5682 | Gastrointestinal disorders | 352 | Sepsis  Gastroenteritis  Syncope | 0.7261- 0.7427 |
| 2 | Skin\_ulcer | 0.5352 | Skin and subcutaneous tissue disorders | 327 | Atrial\_fibrillation  Chest\_pain  Cerebrovascular\_accident | 0.6955 - 0.7192 |
| 3 | Renal\_failure\_chronic | 0.5331 | Renal and urinary disorders | 332 | Cellulitis  Myocardial\_infarction  Cerebrovascular\_accident | 0.6651 - 0.6822 |
| 4 | Orthostatic\_hypotension | 0.5319 | Vascular disorders | 329 | Renal\_failure\_acute  Pulmonary\_embolism  Cellulitis | 0.7044 - 0.7236 |
| 5 | Bladder\_cancer | 0.5260 | Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 327 | Pneumonia  Atrial\_fibrillation | 0.6448 - 0.6986 |
| 6 | Melaena | 0.5244 | Gastrointestinal disorders | 328 | Anaemia  Dyspnoea  Sepsis | 0.6383 - 0.6861 |
| 7 | Encephalopathy | 0.5221 | Nervous system disorders | 385 | Pneumonia  Dehydration | 0.5820 - 0.6325 |
| 8 | Haematoma | 0.5155 | Vascular disorders | 419 | Anaemia  Cellulitis  Syncope | 0.6846 - 0.7114 |
| 9 | Malaise | 0.5074 | General disorders | 339 | Anaemia  Dyspnoea  Sepsis | 0.6207 - 0.6620 |
| 10 | Cardio-respiratory\_arrest | 0.5048 | Cardiac disorders | 523 | Cardiac\_arrest  Asthenia  Gastrointestinal\_haemorrhage | 0.6718 - 0.7188 |
| 11 | Multi-organ\_failure | 0.5046 | General disorders | 545 | Myocardial\_infarction  Syncope  Gastrointestinal\_haemorrhage | 0.7364 - 0.7209 |
| 12 | Ventricular\_tachycardia | 0.5039 | Cardiac disorders | 387 | Pneumonia  Atrial\_fibrillation | 0.6126- 0.6132 |
| 13 | Musculoskeletal\_pain | 0.5014 | Musculoskeletal and connective tissue disorders | 349 | Sepsis  Pleural\_effusion  Syncope | 0.6726 - 0.6906 |
| 14 | Cerebral\_haemorrhage | 0.5 | Nervous system disorders | 490 | Atrial\_fibrillation  Pulmonary\_embolism  Anaemia | 0.7023 - 0.6689 |
| 15 | Ischaemic\_stroke | 0.4979 | Nervous system disorders | 488 | Dehydration  Gastrointestinal\_haemorrhage  Respiratory\_failure | 0.7362 - 0.7542 |
| 16 | Pulmonary\_oedema | 0.4971 | Respiratory, thoracic and mediastinal disorders | 533 | Cardiac\_failure  Cardiac\_arrest  Gastrointestinal\_haemorrhage | 0.6960 - 0.7023 |
| 17 | Arrhythmia | 0.4960 | Cardiac disorders | 504 | Anaemia  Gastroenteritis  Bronchitis | 0.7159 -0.7384 |
| 18 | Erysipelas | 0.4923 | Infections and infestations | 457 | Dyspnoea  Gastroenteritis  Dehydration | 0.6966 - 0.7149 |
| 19 | Atrial\_flutter | 0.4920 | Cardiac disorders | 506 | Chest\_pain  Back\_pain  Gastroenteritis | 0.6801 - 0.7213 |
| 20 | Femoral\_neck\_fracture | 0.4900 | Injury, poisoning and procedural complications | 453 | Syncope  Dehydration  Dyspnoea | 0.7160 - 0.7395 |

We also summarize the category distribution among all serious adverse events, totally there are 26 categories among 38418 unique events are recorded in 20943 clinical serious adverse event arms. Infections and infestations, Gastrointestinal disorder, and Neoplasms benign, malignant and unspecified (incl cysts and polyps) have most frequent serious adverse events recorded, which are 4741, 3298 and 2827. From Death prevalence perspective, besides operational or social circumstances(Surgical and medical procedures - 52.16%, Social circumstances - 49.23%), the top 3 categories are Neoplasms benign, malignant and unspecified (incl cysts and polyps)- 50.56%, , Vascular disorders - 49.06%, General disorders - 46.29%. In each category, Association rules mining finds top 3 confidence events to Death. Some categories didn’t generate higher confidence events to Death, since their confidences are below the threshold.

Table 6 Category

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Category** | **Serious adverse event from death arm**  **(event #)** | **Serious adverse event from all arms (event#)** | **Death arms event#/All arms event#(%)** | **Different Serious Adverse Events# in all arms** | **Top 3 confidence events** |
| Infections and infestations | 26,983 | 68,311 | 39.5% | 4,741 | 0.492341357 Erysipelas  0.488721805 Lung\_infection  0.477777778 Respiratory\_tract\_  infection |
| Gastrointestinal disorders | 21,324 | 49,944 | 42.7% | 3,298 | 0.568181818 Haematemesis  0.524390244 Melaena  0.484771574 Gastric\_ulcer |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 14,239 | 28,162 | 50.56% | 2,827 | 0.525993884 Bladder\_cancer  0.450485437 Lung\_neoplasm\_malignant  0.434482759 Colon\_cancer |
| General disorders | 12551 | 27111 | 46.29% | 2,682 | 0.507374631 Malaise  0.504587156 Multi-organ\_failure  0.466898955 General\_physical\_health\_  deterioration |
| Nervous system disorders | 15,497 | 34,392 | 45.06% | 2,567 | 0.522077922 Encephalopathy  0.5 Cerebral\_haemorrhage  0.49795082 Ischaemic\_stroke |
| Cardiac disorders | 16,244 | 36,503 | 44.50% | 2,245 | 0.504780115 Cardio-respiratory\_arrest  0.503875969 Ventricular\_tachycardia  0.496031746 Arrhythmia |
| Respiratory, thoracic and mediastinal disorders | 13,233 | 31,675 | 41.78% | 1,982 | 0.497185741 Pulmonary\_oedema  0.482871126 Haemoptysis  0.481967213 Epistaxis |
| Vascular disorders | 9,564 | 19,493 | 49.06% | 1,595 | 0.531914894 Orthostatic\_hypotension  0.515513126 Haematoma  0.487551867 Hypertensive\_crisis |
| Surgical and medical procedures | 2,806 | 5,380 | 52.16% | 1,532 |  |
| Blood and lymphatic system disorders | 5,164 | 13,927 | 37.08% | 1,152 | 0.388794567 Leukopenia  0.365384615 Pancytopenia  0.352404643 Thrombocytopenia |
| Renal and urinary disorders | 6,663 | 15,117 | 44.08% | 1,148 | 0.53313253 Renal\_failure\_chronic  0.488479263 Haematuria  0.477922078 Hydronephrosis |
| Skin and subcutaneous tissue disorders | 2,906 | 6,687 | 43.46% | 937 | 0.535168196 Skin\_ulcer  0.357414449 Rash |
| Psychiatric disorders | 4,035 | 12,026 | 33.55% | 897 | 0.436681223 Confusional\_state  0.400419287 Mental\_status\_changes  0.390018484 Anxiety |
| Eye disorders | 2,362 | 5,094 | 46.37% | 812 | 0.475378788 Cataract |
| Reproductive system and breast disorders | 2,491 | 5,560 | 44.80% | 753 | 0.463917526 Benign\_prostatic\_hyperplasia |
| Congenital, familial and genetic disorders | 781 | 1,688 | 46.27% | 564 |  |
| Hepatobiliary disorders | 4,236 | 9,855 | 42.98% | 661 | 0.438625205 Cholecystitis\_acute  0.376460018 Cholecystitis  0.323064113 Cholelithiasis |
| Pregnancy, puerperium and perinatal conditions | 806 | 2,177 | 37.02% | 368 |  |
| Immune system disorders | 1,019 | 2,767 | 36.83% | 314 | 0.372745491 Hypersensitivity |
| Ear and labyrinth disorders | 849 | 1,900 | 44.68% | 208 | 0.441041348 Vertigo |
| Social circumstances | 192 | 390 | 49.23% | 134 |  |

**Two-Adverse Events Confidence to Death**

Combination of two adverse events has higher confidence than each of its single event’s confidence to Death. It’s natural to understand adverse events combination will increase the risk to have life-threatening event. From Table -7, we could see Respiratory\_tract\_infection and Septic\_shock has a very high confidence of 0.783783784 to Death, means when these two events are together, Death has probability of such confidence to occur. Compare to single adverse event confidence in Appendix-4, It’s higher than Respiratory\_tract\_infection’s confidence 0.477777778 and Septic\_shock’s confidence 0.458385093 respectively. In fact, the events pair is most combination of some top frequent single event, because the more frequent to occur as individual, the more often to be “companion” that could be grouped closely. This is not the case in confidence pair, most top confidence of event pairs have very lower frequency, since less frequent event has higher confidence to death, and their combination will have even lower frequency.

Table 7 top 20 confidence double events to Death

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Index** | **Confidence** | **Double Events** | **Frequency(arms#)** | **Target** |
| 1 | 0.783783784 | Respiratory\_tract\_infection  Septic\_shock | 222 | Death |
| 2 | 0.764705882 | Diverticulitis Renal\_failure | 238 | Death |
| 3 | 0.760869565 | Multi-organ\_failure Chest\_pain | 230 | Death |
| 4 | 0.759825328 | Multi-organ\_failure Bronchitis | 229 | Death |
| 5 | 0.756637168 | Appendicitis Renal\_failure | 226 | Death |
| 6 | 0.754237288 | Ischaemic\_stroke Respiratory\_failure | 236 | Death |
| 7 | 0.752988048 | Pneumothorax Dizziness | 251 | Death |
| 8 | 0.752173913 | Ischaemic\_stroke Gastrointestinal\_haemorrhage | 230 | Death |
| 9 | 0.751091703 | Hypokalaemia Cardiac\_failure | 229 | Death |
| 10 | 0.751072961 | Cerebral\_haemorrhage Cardiac\_failure | 233 | Death |
| 11 | 0.751054852 | Multi-organ\_failure Back\_pain | 237 | Death |
| 12 | 0.751004016 | Colon\_cancer Cardiac\_failure | 249 | Death |
| 13 | 0.75 | Haematuria Cardiac\_failure | 252 | Death |
| 14 | 0.75 | Cataract Bronchitis | 236 | Death |
| 15 | 0.747933884 | Septic\_shock Transient\_ischaemic\_attack | 242 | Death |
| 16 | 0.746268657 | Cardiac\_failure Convulsion | 268 | Death |
| 17 | 0.745901639 | Femur\_fracture Septic\_shock | 244 | Death |
| 18 | 0.745833333 | Cardiac\_arrest Depression | 240 | Death |
| 19 | 0.744855967 | Haematuria Cardiac\_arrest | 243 | Death |
| 20 | 0.743902439 | Haematuria Dizziness | 246 | Death |

One typical finding is Cardiac related events are very often paired with other event, and increase the confidence to Death in a very large ratio. We will take Cardiac failure as example, to reveal its influence to Death when it is in pair events. The top 3 serious adverse events which confidence get dramatically changed by combining Cardiac\_failure are Pyrexia, Gastroenteritis and Dehydration. Double confidence to single adverse event. Such discovery could help researchers to predict what are co-exist adverse events with Cardiac failure would bring more danger to patient life. For more adverse events confidence change after grouping with Cardiac failure, please refer to Appendix-6

Table 8 Cardiac\_failure influence to Death from top 20 single to double events, sorted by confidence diff as below.

Cardiac failure -> Death, confidence 0.4312749

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Index | Single Confidence | Single Serious Adverse Event | Category | Double Confidence | Serious Adverse Event Pair | Confidence Diff (Double - Single) |
| 1 | 0.273565145 | Pyrexia | General disorders | 0.617647059 | Cardiac\_failure Pyrexia | 0.344081914 |
| 2 | 0.283976732 | Gastroenteritis | Infections and infestations | 0.6275 | Cardiac\_failure Gastroenteritis | 0.343523268 |
| 3 | 0.311440678 | Dehydration | Metabolism and nutrition disorders | 0.652068127 | Cardiac\_failure Dehydration | 0.340627449 |
| 4 | 0.30982659 | Chest\_pain | General disorders | 0.641723356 | Cardiac\_failure Chest\_pain | 0.331896766 |
| 5 | 0.33295325 | Diarrhoea | Gastrointestinal disorders | 0.664122137 | Cardiac\_failure Diarrhoea | 0.331168887 |
| 6 | 0.358390281 | Deep\_vein\_thrombosis | Vascular disorders | 0.688829787 | Cardiac\_failure Deep\_vein\_thrombosis | 0.330439506 |
| 7 | 0.292903875 | Abdominal\_pain | Gastrointestinal disorders | 0.6201373 | Cardiac\_failure Abdominal\_pain | 0.327233425 |
| 8 | 0.289264414 | Cellulitis | Infections and infestations | 0.616113744 | Cardiac\_failure Cellulitis | 0.32684933 |
| 9 | 0.326267281 | Coronary\_artery\_disease | Cardiac disorders | 0.650837989 | Cardiac\_failure Coronary\_artery\_disease | 0.324570708 |
| 10 | 0.331993569 | Chronic\_obstructive\_pulmonary\_disease | Respiratory, thoracic and mediastinal disorders | 0.656330749 | Cardiac\_failure Chronic\_obstructive\_pulmonary\_disease | 0.32433718 |
| 11 | 0.349192101 | Fall | Injury, poisoning and procedural complications | 0.668639053 | Cardiac\_failure Fall | 0.319446952 |
| 12 | 0.319253438 | Syncope | Nervous system disorders | 0.636761488 | Cardiac\_failure Syncope | 0.31750805 |
| 13 | 0.305860113 | Vomiting | Gastrointestinal disorders | 0.623036649 | Cardiac\_failure Vomiting | 0.317176536 |
| 14 | 0.340069686 | Bronchitis | Infections and infestations | 0.656641604 | Cardiac\_failure Bronchitis | 0.316571918 |
| 15 | 0.367975366 | Back\_pain | Musculoskeletal and connective tissue disorders | 0.683060109 | Cardiac\_failure Back\_pain | 0.315084743 |
| 16 | 0.316793893 | Nausea | Gastrointestinal disorders | 0.62797619 | Cardiac\_failure Nausea | 0.311182297 |
| 17 | 0.33102253 | Pulmonary\_embolism | Respiratory, thoracic and mediastinal disorders | 0.640167364 | Cardiac\_failure Pulmonary\_embolism | 0.309144834 |
| 18 | 0.422321429 | Dizziness | Nervous system disorders | 0.726973684 | Cardiac\_failure Dizziness | 0.304652255 |
| 19 | 0.383116883 | Transient\_ischaemic\_attack | Nervous system disorders | 0.685714286 | Transient\_ischaemic\_attack Cardiac\_failure | 0.302597403 |
| 20 | 0.318303811 | Urinary\_tract\_infection | Infections and infestations | 0.619450317 | Cardiac\_failure Urinary\_tract\_infection | 0.301146506 |

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**Discussion**

Methodology discussion

Clinical meaning

Serious high risk adverse events are frequently associated with patient’s death.

Future work

**Conclusion**

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<http://www.bmj.com/content/323/7304/81?linkType=FULL&resid=323/7304/81&journalCode=bmj>Brossette, S. E., et al. (1998). "Association Rules and Data Mining in Hospital Infection Control and Public Health Surveillance." Journal of the American Medical Informatics Association **5**(4): 373-381.

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Harbarth, S., et al. (2003). "Inappropriate initial antimicrobial therapy and its effect on survival in a clinical trial of immunomodulating therapy for severe sepsis." The American Journal of Medicine **115**(7): 529-535.

Purpose To examine the effect of inappropriate initial antimicrobial therapy on the prognosis of patients with sepsis who were enrolled in a clinical trial of an immunomodulating agent conducted in 108 hospitals in North America and Europe. Methods We assessed initial antimicrobial choice and results of microbiologic cultures in 904 patients who had microbiologically confirmed severe sepsis or early septic shock. If a patient did not receive at least one antimicrobial agent to which the causative microorganisms were susceptible within 24 hours from the diagnosis of severe sepsis, then the initial antimicrobial treatment was considered to be inappropriate. A propensity score that adjusted for factors associated with inappropriate antimicrobial treatment was calculated and included in multivariable models to adjust for confounding. Results A total of 468 patients (52%) had documented bloodstream infection, and 211 patients (23%) received inappropriate initial antimicrobial therapy. Characteristics associated with inappropriate treatment were study enrollment in Europe, admission to surgery, nosocomial infection, infection with multiresistant microorganisms, and fungal or polymicrobial infection (all P &lt;0.05). The 28-day mortality was 24% (168/693) for patients in the adequately treated group versus 39% (82/211) for patients receiving inappropriate initial antimicrobial therapy (P &lt;0.001). After adjusting for comorbid conditions, severity of illness, site of infection, and the propensity score, inappropriate antimicrobial therapy was independently associated with increased mortality (odds ratio = 1.8; 95% confidence interval: 1.2 to 2.6). Conclusion In a large cohort of patients with microbiologically confirmed severe sepsis, appropriate initial antimicrobial therapy was an important determinant of survival. New approaches aimed at improving detection and treatment of early sepsis are needed.

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Mortality and hospitalization rates for pneumonia have increased among older Americans during recent years (1979-86), despite a national commitment to the reduction of premature deaths from pneumonia. A prospective study of deaths and hospitalizations attributable to pneumonia was conducted among 5,474 subjects ages 55 and older who participated in the NHANES I Epidemiologic Followup Study. Prevalent chronic conditions, health behaviors, and nutritional status indicators, measured at baseline, were examined in relation to pneumonia hospitalization and death during 12 years of followup. Mortality and hospitalization rates for pneumonia were higher among men than women, and higher among those ages 65 and older than among those 55-64 of both sexes. Risk of pneumonia death was higher among subjects with a history of congestive heart failure, stroke, cancer, or diabetes. Risk of pneumonia hospitalization was higher among subjects with a history of chronic obstructive pulmonary disease and among men who were current smokers. Daily alcohol consumption did not increase risk of pneumonia in this study population. Four measures of nutritional status were examined taking age, prevalent chronic conditions, and cigarette smoking into account: body mass index, arm muscle area, and serum albumin and hemoglobin levels. Risk of pneumonia death was 2.6 times higher in men in the lowest quartile, compared with men in the highest quartile, of body mass index. Similarly, the risk was 4.5 times higher among men in the lowest quartile of arm muscle area. Risk of death from pneumonia was 3.6 times higher among women in the lowest quartile of serum albumin levels compared with women in the highest quartile. Relative risks for these nutritional status indicators remained elevated after adjusting for age and the medical history risk factors. These risk factors should be taken into account when designing and evaluating pneumonia vaccination trials and community prevention programs.

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Objective This paper intends to apply association rule mining (ARM) to explore the labyrinthian network of ADHD comorbidity, and to examine the practicality of ARM in comorbidity studies using clinic databases. Methods From clinic records of enrollees of Taiwan National Health Insurance (NHI), 18,321 youngsters aged 18 or less with diagnosis of ADHD in 2001 were recruited as case group in this study. And all their clinic diagnoses made from 2000 to 2002, as comorbidity, were categorized according to “The International Classification of Disease, 9th Revision, Clinical Modification” (ICD-9-CM) diagnosis system. For comparison, fourfold non-ADHD controls were recruited from 2001s NHI enrollees on a random base but matched gender and age of cases. ARM was done with Apriori algorithm to examine the strengths of associations among those diagnoses. The support and confidence values of ARM results were examined. Comorbidity rates and relative risk (RR) ratios of both groups of each diagnosis were compared one another. Results ADHD case group has apparently higher risk of comorbidity with psychiatric comorbidity than with other physical illnesses. From results of ARM, developmental delay (DD) appears as an important node between ADHD and anxiety disorder (support: 5.12%, confidence: 97.42%), mild mental retardation (support: 4.42%, confidence: 92.09%) and autism (support: 6.49%, confidence: 94.93%). Conclusions The finding of this study, an important role of DD between ADHD and other psychiatric comorbidity, supports neurological findings in developmental delay of ADHD children's front cortex, as well as some epidemiology findings. This study also demonstrated the practicality of ARM in comorbidity studies using enormous clinic databases like NHIRD.

Thomas, D. R., et al. (2008). "Understanding Clinical Dehydration and Its Treatment." Journal of the American Medical Directors Association **9**(5): 292-301.

Dehydration in clinical practice, as opposed to a physiological definition, refers to the loss of body water, with or without salt, at a rate greater than the body can replace it. We argue that the clinical definition for dehydration, ie, loss of total body water, addresses the medical needs of the patient most effectively. There are 2 types of dehydration, namely water loss dehydration (hyperosmolar, due either to increased sodium or glucose) and salt and water loss dehydration (hyponatremia). The diagnosis requires an appraisal of the patient and laboratory testing, clinical assessment, and knowledge of the patient's history. Long-term care facilities are reluctant to have practitioners make a diagnosis, in part because dehydration is a sentinel event thought to reflect poor care. Facilities should have an interdisciplinary educational focus on the prevention of dehydration in view of the poor outcomes associated with its development. We also argue that dehydration is rarely due to neglect from formal or informal caregivers, but rather results from a combination of physiological and disease processes. With the availability of recombinant hyaluronidase, subcutaneous infusion of fluids (hypodermoclysis) provides a better opportunity to treat mild to moderate dehydration in the nursing home and at home.

Zhihui Luo, P., Guo-Qiang Zhang, PhD, Rong Xu, PhD (2013). "Mining Patterns of Adverse Events Using Aggregated Clinical Trial Results."