Drug Saf (2014) 37:609–616
DOI 10.1007/s40264-014-0195-2

ORIGINAL RESEARCH ARTICLE

Identification of Suicide-Related Events Through Network Analysis of Adverse Event Reports

Alwis Nazir · Takashi Ichinomiya · Nobuteru Miyamura · Yasuaki Sekiya · Yasutomi Kinosada

Published online: 3 July 2014

Abstract

Background In the treatment of depression, it is essential to monitor for early warnings of suicide.

Objective The aim of this study was to identify the symptoms that would suggest a high suicide risk by analyzing data obtained from the US Food and Drug Administration Adverse Event Reporting System (FAERS) of selective serotonin reuptake inhibitors.

Methods Using FAERS reports from 1997 to the second quarter of 2012, we constructed the co-occurrence network of adverse events. From this network, we extracted the events that were strongly connected to suicidal events (suicidal attempts, suicidal ideation, suicidal behavior, and complete suicide) by means of the community detection method.

Results We succeeded in obtaining a list of suicide-related adverse events. Owing to the randomness inherent in the algorithms of community detection, we found that the obtained list differed according to each trial of analysis. However, the lists we derived show considerable efficiency in identifying suicidal events.

Conclusion The network analysis appears to be a promising method for identifying signals of suicide.

Key Points

Using network analysis, we constructed a list of suicide-related adverse events from the US Food and Drug Administration Adverse Events Reporting System.

With that list, we were able to qualitatively estimate the risk of suicide.

Though this method presents problems, such as high numbers of false-positive results and overly long symptom lists, these may be countered by improving the modularity detection algorithm and network construction and by using different signal detection methods.

A. Nazir (✉) · T. Ichinomiya · N. Miyamura · Y. Sekiya · Y. Kinosada
The United Graduate School of Drug Discovery and Medical Information Sciences of Gifu University, Yanagido 1-1, Gifu 501-1194, Japan
e-mail: alwis.nazir@gmail.com

A. Nazir
State Islamic University of Sultan Syarif Kasim Riau, Jl. H.R.Soebrantas No.155 KM 18, Simpang Baru Panam, Pekanbaru 28293, Indonesia

T. Ichinomiya · Y. Kinosada
Department of Biomedical Informatics, Gifu University School of Medicine, Yanagido 1-1, Gifu 501-1194, Japan

1 Introduction

Suicide is a critical symptom of depression [1]. To reduce suicide deaths, it is essential to estimate accurately the suicide risk of patients and to give proper treatment. Researchers have extensively investigated suicide risk factors, such as acute mood episodes, personal history, and family history [2, 3]. However, more reliable medical signs that indicate suicidal risk are required.

The aim of this study was to identify the symptoms strongly related to suicide. To this end, we analyzed

adverse event reports on selective serotonin reuptake inhibitors (SSRIs). SSRIs are the most widely used antidepressant worldwide. They are believed to decrease the risk of suicide [4]; however, even if depressive patients take SSRIs properly, their suicide risk is still greater than that of individuals without depression. Among the reported adverse events of SSRIs are suicidal ideation, suicidal attempt, suicidal behavior, and complete suicide. These adverse events related to suicide provide useful information toward estimating suicide risk.

In this study, we attempted to compile a list of the adverse events that are strongly related to suicide. For this purpose, we analyzed the reports in the US Food and Drug Association (FDA) Adverse Event Reporting System (FAERS). FAERS is the spontaneous reporting system of adverse events and is widely used in pharmacovigilance analysis [5–7]. To analyze FAERS data, we employed the method of community detection in networks.

Network analysis has been extensively adopted in research into social systems, biological processes, and computer systems [8]. In network analysis, a complex system is modeled using a network—the set of nodes and the set of edges that connect those nodes. For example, in modeling a social network, such as sexual contact, each individual is modeled as a node and edges are made among the people who have sexual contacts [9]. In network analysis of a gene regulatory network, each gene is taken as a node and an edge is placed between two genes if one gene regulates the other.

The detailed analysis of such networks provides considerable interesting information. For example, it has been demonstrated that social networks usually have a small number of important nodes called hubs [9]. This property plays an important role in strategic vaccination because the spreading of a virus may be effectively prevented by focusing vaccination efforts on such hubs [10]. From an analysis of the gene regulatory network of *Escherichia coli* and a yeast species, it was shown that gene regulatory networks have several patterns, called network motifs [11]. These motifs display some particular functions, such as creating pulse when the environment changes. Network analysis also has promising applications in medicine. Barabási [12] proposed a network called the diseasome, in which the nodes are diseases and the edges are the connections between two diseases. He believed that this network was useful in predicting the progress of diseases and in identifying the common causes of different diseases.

In the present study, we constructed the network of symptoms reported as adverse events in FAERS and extracted the symptoms that are strongly correlated with suicidal symptoms. Compared with other data mining methods, such as association analysis and Bayesian analysis, network analysis presents several advantages and disadvantages. The major advantage with network analysis is that it can analyze indirect connections. Because it addresses the whole network structure, it can capture hidden relations that would fail to be recognized by association analysis or Bayesian analysis, which deal with the correlation among a restricted number of objects. However, the method of network analysis is still under development. There is no established method for analyzing a network, and many new methods are proposed every year. With FAERS data, several studies have applied association analysis or Bayesian analysis [13, 14], but none have been based on network analysis.

In the present study, we constructed a symptom network of adverse events. We conducted modularity-based community detection [15] to extract the list of suicide-related adverse events that were believed to have a strong connection with suicidal events: suicidal behavior, suicidal ideation, suicidal attempts, and complete suicide. We investigated the relationship between suicide risk and those events.

2 Methods

2.1 Data Preparation

We obtained the original dataset of FAERS containing the reports received by the FDA from 1997 to the second quarter of 2012. From this dataset, we extracted reports of adverse events in which SSRI involvement was suspected. Each report in FAERS is composed of a unique identification number, a list of drugs that the patient took, and a list of patient reactions. The names of reactions are coded by the preferred term (PT) defined by the *Medical Dictionary for Regulatory Activities* (MedDRA®).[1] Though the terms defined by MedDRA® depend on the version employed, we neglected such differences in our analysis; since most PTs did not change between 1997 and 2012, we believed that these differences would not lead to severe errors in our study. However, the names of drugs are not standardized in FAERS, drugs may appear under their generic or proprietary names. For the standardization of drug names, we used American Hospital Formulary Service (AHFS) *Drug Information 2010* [16] and DrugBank [17]. DrugBank was employed to link the generic and proprietary names of each drug; AHFS drug information

[1] MedDRA®, the *Medical Dictionary for Regulatory Activities* terminology, is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The MedDRA® trademark is owned by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) on behalf of ICH.

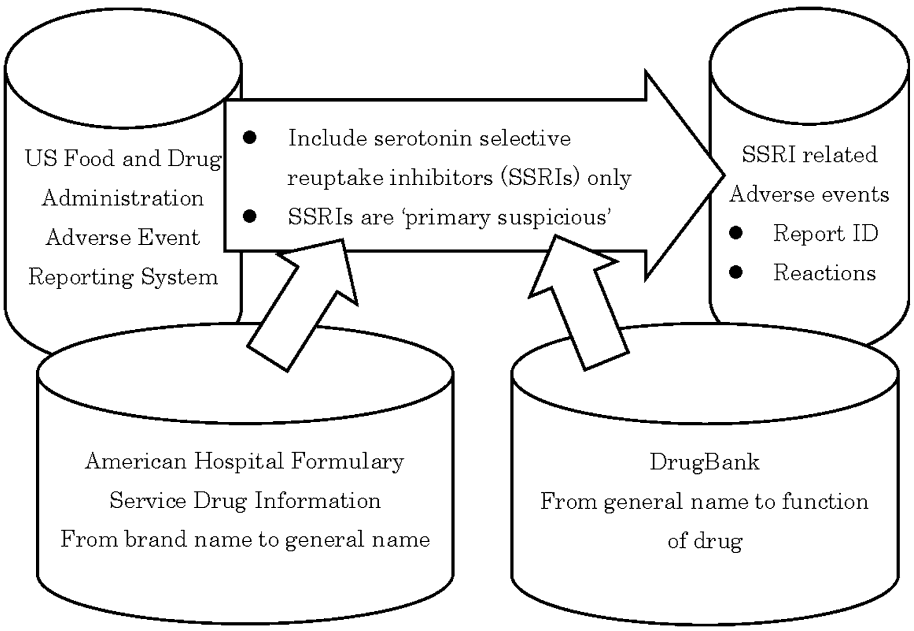

Fig. 1 Construction of databases of adverse events of selective serotonin reuptake inhibitors (SSRIs)

Table 1 Summary of the reports used in the analysis

Group ID	Number of reports	Reports including suicidal events
1	21,497	2,697
2	21,497	2,652

was used to combine the generic drug name with its function, such as 'SSRI'.

Each FAERS report includes such details as patient demographic information, patient outcome, and prime suspect for the adverse event. From those data, we extracted reports related to SSRIs as follows. First, we selected reports in which only a single drug was used and the drug was citalopram, escitalopram, fluoxetine, paroxetine, or sertraline. From this list, we selected those reports in which SSRIs were regarded as the prime suspect. In this way, we produced a list that contained the report identification number and the patient reactions. A schema of these procedures is presented in Fig. 1.

The resulting reports were randomly divided into two groups. Group 1 was used to construct the adverse event networks and compile a list of suicide-related adverse events. Group 2 was used for quantitative evaluation of this list. The number of reports appears in Table 1.

2.2 Network Analysis

From the data obtained with the procedures described in Sect. 2.1, we constructed the network of adverse events in the same manner as Barabási constructed the diseasome network [12]. With our network, the reactions were represented as nodes; the edge between nodes represented the co-occurrence of adverse events, whose weight was given by Pearson's correlation σ_{AB}, defined by

$$\sigma_{AB} = (Nn_{AB} - n_A n_B)/\sqrt{n_A n_B (N - n_A)(N - n_B)},$$

where n_A, n_B, n_{AB}, and N represent the numbers of reports that indicate adverse event A, that indicate adverse event B, that report the adverse events of both A and B, and the total number of reports, respectively. σ_{AB} can take both positive and negative values, but we made an edge only when σ_{AB} was positive; this was because community detection fails if the edge weight is negative. This process is illustrated in Fig. 2. At this stage, we removed isolated nodes; that is, adverse events that have no positive correlation with others.

Using modularity-based community detection, the obtained network was divided into small groups called communities [15]. We derived the list of suicide-related adverse events, which were those events that were in the same community as suicidal events.

In modularity-based community detection, the best partitioning of the network is that with maximal modularity. Modularity is defined using the following equation:

$$Q = \frac{1}{2m}\sum_{ij}\left[\sigma_{ij} - \frac{k_i k_j}{2m}\right]\delta(c_i, c_j),$$

where σ_{ij} is the weight of the edge between node i and j, $k_i = \sum_l \sigma_{il}$, $k_j = \sum_l \sigma_{jl}$, $m = \frac{1}{2}\sum_{ij}\sigma_{ij}$, and $\delta(c_i, c_j)$ is 1 if node i and j belong to the same community and 0 otherwise. From an intuitive perspective, modularity is the characteristic that indicates the average density of the internal edges in each community. To understand the

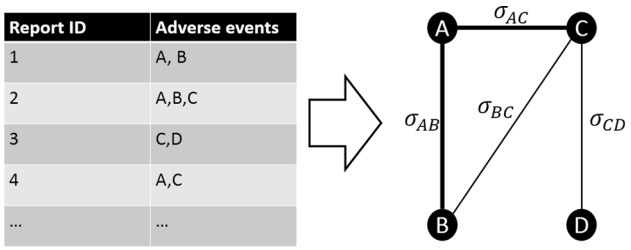

Fig. 2 Construction of adverse-event network

meaning of modularity more clearly, consider two nodes, i and j, in the same community. If there is an edge between these nodes, $\sigma_{ij} - \frac{k_i k_j}{2m}$ is positive provided that σ_{ij} is sufficiently large. Conversely, if there is no edge between them, $\sigma_{ij} - \frac{k_i k_j}{2m} = -\frac{k_i k_j}{2m}$ is always negative. Consider, for example, the network represented in Fig. 3a, where for simplicity the setting is $\sigma_{ij} = 1$. In the partitioning depicted in Fig. 3b, nodes B, C, and D are members of the same community, whereas node A is not. In this case, we do not sum the pairs of nodes (A, B), (A, C), and (A, D) in calculating modularity because A belongs to a different community from the others. However, if we divide the network as in Fig. 3c, these three pairs provide contributions to the modularity. The existence of edges (A, B) and (A, D) increases the modularity, though the absence of edge (A, C) decreases it. In Fig. 3, the positive contribution from the existence of the edges exceeds the negative one from the absence of one edge. This implies that nodes B and C intermediate the connection between A and C so strongly that they compensate for the absence of a direct connection. Therefore, we would conclude that nodes A and C are in the same cluster.

Two points should be noted here. First, high computational power is necessary to obtain the best partitioning with a large network. To overcome this difficulty, several methods have been proposed [18–21]. In the present study, we applied the algorithm developed by Blondel et al. [21]. Our approach consisted of two phases. In the first phase, we decomposed the network into many small communities. Then, we aggregated the nodes within the same community and constructed a new network, in which the nodes were the small communities obtained in the first phase. Repeating these two processes iteratively, we obtained the community structure of networks. This algorithm is sufficiently fast for application, though it is stochastic: we obtained a slightly different result with each trial of community detection. In Sect. 2.3, we present the results of 20 community detection trials.

Second, in modularity-based community detection, we often encounter the problem of limit of resolution: we fail to identify small communities [22]. This problem may be partially solved by slightly modifying the definition of modularity [23]. In this approach, we employ the tunable parameter of resolution, which controls the accuracy of community detection. The exact definition of the resolution is provided by Lambiotte et al. [23]. In our analysis, we set the resolution parameter as 1.0. These analyses were conducted using Gephi [24]. The process is depicted in Fig. 4.

2.3 Evaluation of Suicide-Related Adverse Events

There may be more than one suicide-related adverse event, and it is natural to assume that a patient has a higher suicide risk if they have more suicide-related adverse events. Therefore k, the number of suicide-related adverse events of a patient, can be taken as the control parameter in risk evaluation. We estimated the risk as follows. First, we determined the proportion of patients who had suicidal events and k (suicide-related adverse events). Second, we plotted the receiver-operating characteristic (ROC) when k varied between 1 and 50. The ROC reflects the effectiveness of suicide-related adverse events as indicators.

These evaluations were conducted with the data for Group 2. Those data were not used for the first network analysis.

3 Results

The network of adverse events of SSRIs had 3,795 nodes. Using the community detection method described in Sect. 2.2, we obtained lists of suicide-related adverse events. As noted above, the algorithm for community detection is stochastic, and we obtained a different list for each run of the analysis. A typical list appears in Table 2, which includes 141 events. We conducted network analysis 20 times, and the number of items on the list varied from 141 to 290 events. The lists included both well known risk factors, such as social problems and stress, and other adverse events, such as cardiorespiratory arrest and gastric ulcer.

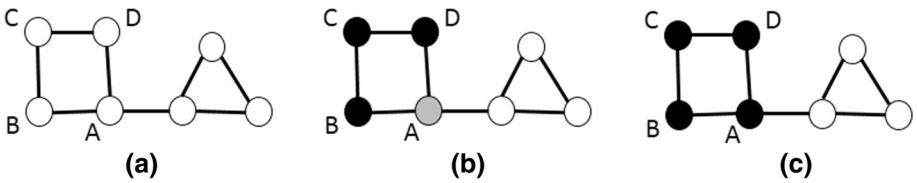

Fig. 3 Modularity-based partitioning of the network (**a**). Partitioning (**b**) [$Q = 13/32$] gives lower modularity (**c**) [$Q = 33/64$]

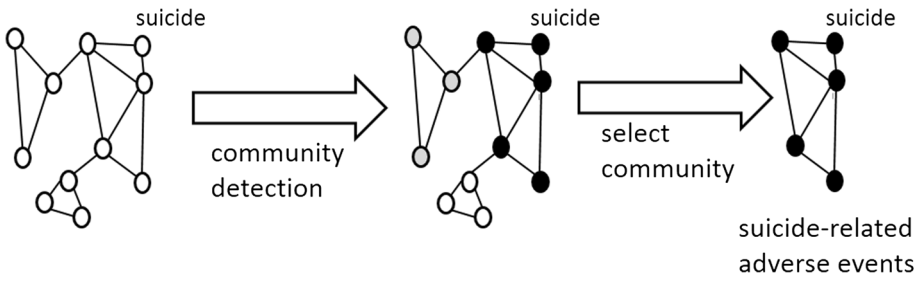

Fig. 4 Process of extracting suicide-related adverse events

Table 2 List of suicide-related adverse events obtained by analysis

Abnormal behavior	Activation syndrome	Adverse drug reaction	Adverse event
Affect lability	Affective disorder	Agoraphobia	Akathisia
Alcohol poisoning	Alcohol use	Anger	Anhedonia
Antisocial behavior	Apathy	Asphyxia	Balance disorder
Bipolar disorder	Bipolar i disorder	Breast cancer	Cardio-respiratory arrest
Cognitive disorder	Coma	Communication disorder	Condition aggravated
Crying	Decreased appetite	Decreased interest	Delusion
Dementia	Depersonalization	Depressed mood	Depression
Derealization	Disease recurrence	Disinhibition	Dissociation
Drug abuse	Drug abuser	Drug administration error	Drug dose omission
Drug effect decreased	Drug ineffective	Drug interaction	Drug intolerance
Drug screen false positive	Drug screen positive	Economic problem	Educational problem
Electric shock	Emotional disorder	Emotional distress	Fear
Fear, focus	Feeling abnormal	Feeling of despair	Flashback
Flat affect	Formication	Gastric disorder	Gastric ulcer
General physical health deterioration	Gun shot wound	Hallucination, auditory	Hallucination, visual
Hallucinations, mixed	Homicidal ideation	Homicide	Hostility
Hypersomnia	Ill-defined disorder	Immobile	Impaired work ability
Imprisonment	Impulsive behavior	Incorrect dose administered	Increased appetite
Indifference	Injury	Injury asphyxiation	Intentional overdose
Intentional self-injury	Judgment impaired	Laceration	Legal problem
Libido increased	Logorrhea	Loss of employment	Loss of libido
Major depression	Mania	Marital problem	Mental disorder
Mental impairment	Mental status changes	Mood altered	Mood swings
Multiple drug overdose	Murder	Muscular weakness	Musculoskeletal pain
Negative thoughts	Nervous system disorder	No adverse drug effect	Obsessive thoughts
Obsessive-compulsive disorder	Overdose	Panic attack	Panic disorder
Paranoia	Personality change	Personality disorder	Pharmaceutical product complaint
Physical assault	Poor quality sleep	Post-traumatic stress disorder	Psoriasis
Psychiatric symptom	Psychomotor hyperactivity	Psychotic disorder	Refusal of treatment by patient
Relationship breakdown	Respiratory arrest	Restlessness	Self esteem decreased
Self-injurious behavior	Self-injurious ideation	Shock	Skin laceration
Social avoidant behavior	Social problem	Stress	Tearfulness
Tension	Theft	Therapeutic response decreased	Therapeutic response unexpected with drug substitution
Thinking abnormal	Tic	Treatment noncompliance	Violence-related symptom
Withdrawal syndrome			

It should be noted that suicide-related adverse events do not always have a high correlation with suicidal events. Table 3 presents the top ten adverse events that had a high Pearson's correlation with suicidal events. Interestingly, agitation, which showed the highest such correlation, is not in Table 2. This is because agitation also has a high

correlation with other events. For example, agitation had a correlation of 0.462 with a confusional state, 0.349 with a disturbance in attention, and 0.328 with tremors. As a result of these high correlations, agitation was clustered into a different community from suicidal events.

By contrast, cardiorespiratory arrest appeared among the suicide-related adverse events, though it had a low Pearson's correlation with suicidal events (0.03 for complete suicide, 0.008 for suicide ideation). However, this event is listed as suicide-related because it has a relatively high correlation with other suicide-related events. Cardiorespiratory arrest has a low correlation with other events. The greatest correlation was 0.096, which was the correlation for cardiac arrest. Cardiorespiratory arrest has a fairly high correlation with suicide-related events, such as flat affect (0.075), social avoidance behavior (0.06), and restlessness (0.038). It is natural to assume that cardiorespiratory arrest is related to suicidal behavior because suicidal attempts often result in cardiorespiratory arrest. Network analysis succeeded in revealing this relationship, which could not be identified using standard statistical analysis.

In the following section, we evaluate the effectiveness of the lists obtained in evaluating the risk of suicide. Unless otherwise indicated, the dataset for Group 2 was used for the evaluation.

First, we plotted the population of suicidal events as the function, defined in Sect. 2.3 (Fig. 5). In that figure, the results of 20 trials of community detection are indicated by open triangles. It is evident in Fig. 5 that the results allow a division into groups. In 12 times among 20 trials of community detection, we obtained lists of adverse events that were strongly related to suicide: in those cases, if a patient had one suicide-related adverse event, the probability that they would also have a suicidal event was about 25 %. That was about twice the figure for a subject with no suicide-related adverse events. The probability of suicidal events increased with an increase in k and became about 60 % at $k = 5$. These results indicate that the obtained adverse events displayed a strong relationship with suicidal events. Other lists, such as those obtained eight times among 20 trials of community detection, were more weakly related with suicidal action. In those cases, the proportion of suicidal events was less than 20 % at $k = 1$; the local maximum was approximately 40 % at k of about 10. This was due to the list of suicide-related adverse events in such cases being excessively long. Each of those lists included over 200 adverse events, whereas the length of 'high-performance' lists had 140–200 items. Therefore, we conclude that those 'low-performance' lists included events that held only a weak connection with suicidal events.

Figure 5 also presents a plot of the proportion with the following: when the dataset for Group 1 was used instead of that for Group 2 (open circles); when all adverse events were employed rather than suicide-related adverse events (closed circles); and when 200 adverse events were used with a high Pearson's correlation with suicidal events (closed triangles). Clearly, there is no quantitative difference between the results obtained with the dataset for Group 1 and that for Group 2. In both cases, there were low- and high-performance lists. Compared with the results obtained with the suicide-related adverse event lists, the performance of the list for all adverse events was low. For example, the proportion of suicidal events at $k = 5$ was less than 0.2, whereas the high-performance list gave k of about 0.6. Interestingly, when we used the list of 200 adverse events with a high Pearson's correlation, the

Table 3 Top ten adverse events with a high Pearson's correlation with suicidal events

Suicidal event	Related event	Pearson's correlation
Suicidal ideation	Agitation	0.21
Suicidal ideation	Fatigue	0.151
Suicidal ideation	Crying	0.138
Suicidal ideation	Nervousness	0.132
Suicidal ideation	Nausea	0.123
Suicidal ideation	Drug withdrawal syndrome	0.122
Suicidal attempt	Non-accidental overdose	0.104
Suicidal behavior	Alcohol poisoning	0.075
Suicidal ideation	Restlessness	0.068
Suicidal attempt	Agitation	0.061

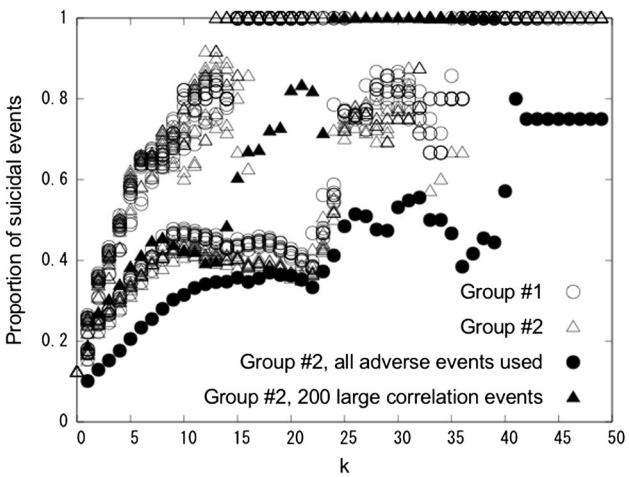

Fig. 5 Proportion of suicidal events as a function of k obtained by 20 trials of community detection. *Open circles*, *open triangles*, *closed circles*, and *closed triangles* represent the results obtained from the analysis of the dataset in Group 1 using suicide-related events, that of the dataset in Group 2 using suicide-related events, that of the dataset in Group 2 using all adverse events, and that of the dataset in Group 2 using 200 adverse events with a high Pearson's correlation, respectively

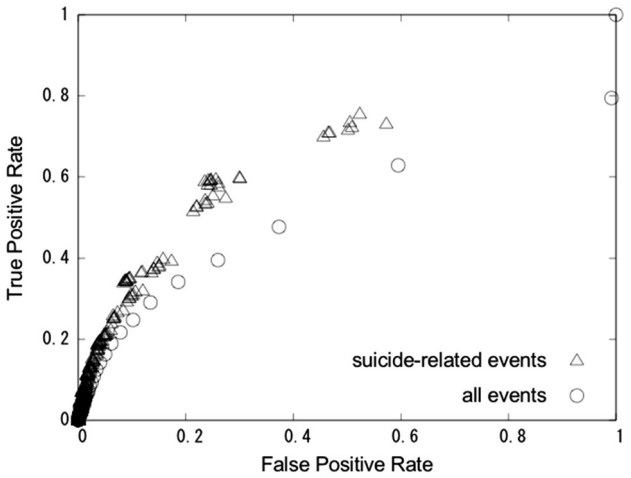

Fig. 6 Receiver operating characteristic curve obtained with the dataset in Group 2 for suicide-related adverse events (*triangles*) and for all adverse events (*circles*)

performance was better than the low-performance list; it was, however, worse than the high-performance list. Particularly, if k was under 15, the performance of the list with high Pearson's correlation was almost the same as with the low-performance list. These results suggest that community detection may capture the hidden relationship better than the simple Pearson's correlation.

We plotted the ROC to investigate the false-positive and true-positive rates. For each list obtained with 20 trials of modularity analysis, we calculated the true-positive and false-positive rates when we varied k from 0 (no accompanying adverse events) to 50. The result is indicated by the triangles in Fig. 6. The results obtained with each list were consistent: we obtained a true-positive rate of 60 % and a false-positive rate of 20 %. Using the trapezoidal rule for calculation, we obtained an area under curve (AUC) of 0.648–0.697 (0.681 on average). To demonstrate that our method effectively extracted suicide-related adverse events, we plotted the ROC when all adverse events were taken to be suicide-related (the circles in Fig. 6). The ROC obtained with our network analysis clearly showed a better performance than the one without network analysis, which resulted in an AUC of 0.529. This result suggests that our method was successful in effectively extracting suicide-related adverse events.

4 Discussion

The method adopted in the present study will be helpful in analyzing other diseases or adverse events. Compared with other analysis techniques, such as association analysis and Bayesian analysis, an advantage of our method lies in its ability to capture the indirect connection between symptoms; for example, cardiorespiratory arrest and suicide. Another advantage is that we were able to control the sensitivity and specificity. With association analysis and Bayesian analysis, it is possible to investigate the relationship among one or a few symptoms. In contrast, our method identifies the group of symptoms that belong to the same community with target symptoms. With this approach, sensitivity or specificity can be modified by stipulating the number of symptoms, k, and we were able to adjust for maximal expected patient benefit.

However, our method presents several problems, and clinical application will demand further improvement. First, the list of symptoms we obtained was too long for clinical use. The smallest set of symptoms we obtained included over 140 symptoms. For practical application, that should be reduced to fewer than 20. This can be achieved in several ways. Refinement of the community detection algorithm may help in reducing that list. The modularity-based method is standard for community detection, but it is not the only approach. Different methods [18–20] may offer better performance for extracting suicide-related adverse events. Adjusting the resolution will also help control the size of the adverse event list. Such approaches will result in a smaller set of suicide-related events. It should be noted that our method for network construction is not unique. For example, Barabási constructed a two-diseasome network—one based on Pearson's correlation and the other on relative risk [12]. The relative risk-based network may provide a better indicator of suicide. Further study is required on the way to construct a network of symptoms and to detect communities.

The second problem with our study is the high false-positive detection rate. To surmount this problem, it would be useful to apply different signal detection techniques in combination with the community detection method. For example, a method based on the likelihood ratio test has been demonstrated to control false-positive rates [25]. Many other algorithms of signal detection exist, such as proportional reporting ratio, reporting odds ratio, simplified Bayes, multi-item gamma Poisson shrinker, and Bayesian confidence propagation neural networks [26]. Applying these methods in combination with community detection will reduce the false-positive rate and increase the AUC.

Finally, we note that our result shows only correlation, not causation. For example, items such as cardiorespiratory arrest and gunshot wounds in our lists should not be taken as the cause but the result of suicidal behavior. We cannot determine whether or not overdose is the result of a suicidal attempt. Some of the adverse events, such as logorrhea and tics, seem to have no apparent relation to suicide. This problem is intrinsic in the analysis of spontaneous adverse reports. Investigating the cause of suicidal events demands another approach, such as a prospective cohort study.

5 Conclusion

In this study, we constructed lists of suicide-related adverse events from the FAERS using network analysis. We found that the more listed adverse events a person possessed, the greater the risk of suicide. This result suggests that such lists allow a qualitative estimation of the risk of suicide. Though our method presents problems, such as the high level of false-positive results and excessively long symptom lists, such drawbacks may be countered by refining the modularity detection algorithm, modifying the means of network construction, and applying different signal detection methods.

Conflict of interest statement No external sources of funding were used in the preparation of this study. Alwis Nazir, Takashi Ichinomiya, Nobuteru Miyamura, Yasuaki Sekiya and Yasutomi Kinosada have no conflicts of interest that are directly relevant to the contents of this study.

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