A novel method for analyzing the contribution of risk factors for the severity of Xiyanping Injection’s adverse events, 2004-2020

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Abstract

Objectives: Based on previous studies, analyze risk factors (age and combination) contributing to the severity of Xiyanping Injection’s (XYP) adverse events (AEs) by a novel method.

Methods: Total AEs linked to the use of XYP injection were classified as general or serious and analyzed in the China National Adverse Drug Reaction Monitoring Information System (2004-2020). Data were analyzed with respect to age and herb-drug combination (ribavirin, ceftriaxone, penicillin sodium, ambroxol hydrochloride, clindamycin, cefoxitin sodium, azithromycin, ceftazidime, amoxicillin sodium and clavulanate potassium, levofloxacin hydrochloride, cefazolin sodium pentahydrate and cefuroxime) by variable importance for projection (VIP).

Results: 28599 AEs (general27037, severe 1562) relating to XYP’s combination were included. Based on the VIP value and correlation coefficient, the results showed that in 0-6 years old, XYP -ribavirin, -ceftazidime and -ambroxol hydrochloride combination indicate positive impact on the severity of AEs.

In 7-17 years old, XYP-cefoxitin sodium and -azithromycin combination tended to have general AEs. XYP-cefazolin sodium pentahydrate and -amoxicillin sodium and clavulanate potassium combination tended to have severe AEs. In 18-40 years old, XYP-ribavirin and -clindamycin combination tended to have severe AEs. In 41-65 years old, Under the influence of XYP-cefatriaxone, -penicillin sodium and -cefoxitin sodium combination, it tended to have severe AEs. In 65 years old, XYP-RB, clindamycin and -amoxicillin sodium and clavulanate potassium combination tended to have general AEs. Under the influence of XYP-cefoxitin sodium and -ceftazidime combination, it tended to increase the severity of AEs. The two groups had the same impact on the severity of AEs.

Conclusions: VIP scores are useful in evaluating the risk factors affecting outcome indicators in clinical studies. It is recommended that clinical practitioners should pay attention to the metabolic characteristics of different age groups and strictly implement standardized operations such as medication interval and flushing.

1 Introduction

Xiyanping injection (XYP) is a kind of traditional Chinese medicine (TCM) preparation made from andrographolide by sulphonation modification, which has the effects of relieving cough and dysentery. It is widely combined with western medicine to treat bronchitis, tonsillitis, bacterial dysentery and other diseases. Eliminating the effect of COVID-19, XYP has the highest sales of TCM (2019) for respiratory diseases in China. The sales volume of XYP was 3.122 billion yuan, far exceeding that of other drugs, accounting for 4.34%, shown in Figure 1.

In our previous studies, age and XYP-Ribavirin (RB) combination were be potential risk factors for the severity of XYP related adverse events (AEs). But what is the contribution of risk factors to the severity of AEs? In other studies, age is considered be the key factor affecting the occurrence of adverse reactions. Does the combinations have different effects in different age groups? This will indicate the clinically safety of medication in different age groups. Therefore, in order to further explore the influence of age and different drug combinations on the severity of AEs, a novel method was introduced to analyze the severity of AEs.

The VIP (variable importance for projection) score first published by Wold in 1993 measures explicative power of predictor variables with respect to the response variable which basing on the partial least squares regression. The VIP was introduced to calculating the contribution of risk factors for the severity of AEs. It is expected to drug-herb combination be reasonably applied within the safety range to ensure clinical safety.

2 Methods

2.1 Inclusion and exclusion criteria

AEs of XYP in the National Adverse Drug Reaction Monitoring Information System (NADRMIS) from January 2004 to December 2020 were selected. Independent variables of interest were age and combination. In order to analyze the potential risk, common antibacterial/antiviral agents were selected for analysis, including Ribavirin (RB), Ceftriaxone (CTR), Penicillin sodium (PS), Ambroxol (AH), Clindamycin (DA), Cefoxitin sodium (FOX), Azithromycin (AZM), Ceftazidime (CAZ), amoxicillin sodium and clavulanate potassium (AMC), Levofoxacin Hydrochloride (LEVH), cefazolin sodium pentahydrate (CSP) and Cefuroxime (CEF). More than two drugs in combination have a more complex relationship, which is not involved in this study. Cases without key factors were excluded. Personal information was excluded from our dataset for confidentiality consideration.

2.2 Definition of severity of AEs

We classified each AE based on the NADRMIS measures. Severe AEs were defined as any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of an existing hospital stay, results in persistent or significant disability/incapacity, cancers and congenital anomalies or birth defects, or is life threatening. The other AEs were considered as general issues.

2.3. Data coding
Cases were stratified by age group as follows: children (0–6 years), juvenile (7–17 years), young (18–40 years), middle-aged (41–65 years), older (>65 years). This association may indicate the drug interaction's risk when AEs in combination with two drugs are reported more frequently \(^{12}\).

### 2.4. Statistical analysis

VIP can calculate the contribution degree of each input information to the prediction model to judge the importance of single independent variable (risk factor) in explaining the dependent variable (the severity of AEs). The input variables of the model are age and 12 XYP-combination groups. The output is the severity of AEs. The equation (1) is for details.

\[
VIP_j = \frac{k \sum_{h=1}^{m} r^2(y_j, c_h)w_{hj}^2}{\sqrt{\sum_{h=1}^{m} r^2(y_j, c_h)w_{hj}^2}} 
\]

Equation (1)

The \(k\) is independent variable; \(c_h\) is the principal component of relevant independent variables, \(r^2(y_j, c_h)\) is the correlation coefficient between the dependent variable and the principal component, indicating the explanatory ability of the principal component to \(y\) (the severity of AEs), and \(w_{hj}\) is the weight of the independent variable on the principal component.

The value of VIP score which is greater than 1 is the typical rule for selecting relevant variables\(^{(49)}\) and can be considered important in given model, the contribution of this variable to \(Y\) (the severity of AEs) is great. If the explanatory effects of the respective variables (age, herb-drug combination) on \(y\) (the severity of AEs) are the same, the VIP values of all independent variables are 1.

The correlation coefficient indicates the contribution direction of VIP value. If the correlation coefficient (Coeff) > 0, the factor tends to increase the severity of AEs. If the Coeff < 0, the factor tends to reduce severity. If the VIP value is 0 or the drug is not used, it will not be displayed. The details were showed in Figure 2.

### 3 Results

#### 3.1 Identified studies and characteristics

We identified a total of 38018 cases of AEs related to the use of XYP injection in NADRMI. Of these, 9419 cases did not provide any AEs indices or other reasons were thus excluded, resulting in 28599 cases with eligible data (Figure 3). There are 27037 general AEs and 1562 Severe AEs. A full list of the distribution of AEs in different age group is provided in Table 1.
### Table 1 Distribution of AEs in different age group

<table>
<thead>
<tr>
<th></th>
<th>The first age group</th>
<th>The second age group</th>
<th>The third age group</th>
<th>The fourth age group</th>
<th>The fifth age group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>General AEs</td>
<td>Severe AEs</td>
<td>General AEs</td>
<td>Severe AEs</td>
<td>General AEs</td>
</tr>
<tr>
<td>XYP</td>
<td>13378(0.96)</td>
<td>612(0.04)</td>
<td>2209(0.94)</td>
<td>129(0.06)</td>
<td>3344(0.94)</td>
</tr>
<tr>
<td>RB</td>
<td>99(0.92)</td>
<td>10(0.09)</td>
<td>7(1)</td>
<td>0(0)</td>
<td>10(0.91)</td>
</tr>
<tr>
<td>CTR</td>
<td>190(0.95)</td>
<td>11(0.05)</td>
<td>22(0.96)</td>
<td>1(0.04)</td>
<td>10(0.91)</td>
</tr>
<tr>
<td>PS</td>
<td>11(1)</td>
<td>0(0)</td>
<td>4(1)</td>
<td>0(0)</td>
<td>7(0.88)</td>
</tr>
<tr>
<td>AH</td>
<td>49(0.93)</td>
<td>4(0.08)</td>
<td>3(1)</td>
<td>0(0)</td>
<td>0(0)</td>
</tr>
<tr>
<td>DA</td>
<td>60(0.94)</td>
<td>4(0.06)</td>
<td>15(0.94)</td>
<td>1(0.06)</td>
<td>36(0.9)</td>
</tr>
<tr>
<td>FOX</td>
<td>124(0.95)</td>
<td>6(0.05)</td>
<td>25(1)</td>
<td>0(0)</td>
<td>16(1)</td>
</tr>
<tr>
<td>AZM</td>
<td>191(0.96)</td>
<td>8(0.04)</td>
<td>42(1)</td>
<td>0(0)</td>
<td>31(0.91)</td>
</tr>
<tr>
<td>CAZ</td>
<td>156(0.93)</td>
<td>11(0.07)</td>
<td>18(0.90)</td>
<td>2(0.10)</td>
<td>9(1)</td>
</tr>
<tr>
<td>AMC</td>
<td>146(0.96)</td>
<td>6(0.04)</td>
<td>16(0.89)</td>
<td>2(0.11)</td>
<td>8(1)</td>
</tr>
<tr>
<td>LEVH</td>
<td>2(1)</td>
<td>0(0)</td>
<td>0(0)</td>
<td>0(0)</td>
<td>0(0)</td>
</tr>
<tr>
<td>CSP</td>
<td>57(0.95)</td>
<td>3(0.05)</td>
<td>5(0.71)</td>
<td>2(0.29)</td>
<td>4(1)</td>
</tr>
<tr>
<td>CEF</td>
<td>221(0.97)</td>
<td>8(0.03)</td>
<td>47(0.96)</td>
<td>2(0.04)</td>
<td>45(0.92)</td>
</tr>
</tbody>
</table>

n = the percentage was calculated by dividing the total number of cases by the number of AEs cases for each level.

AH, Ambroxol hydrochloride; AMC, Amoxicillin sodium and clavulanate potassium; AZM, Azithromycin; CAZ, Ceftizidime; CEF, Cefuroxime; CSP, Cefazolin sodium pentahydrate; CTR, Cefatriaxone; DA, Clindamycin; FOX, Cefoxitin sodium; LEVH, Levofloxacin Hydrochloride; PS, Penicillin sodium

### 3.2 VIP analysis of risk factors on age and herb-drug combination

Age and 12 combination groups were included in VIP analysis. The detailed results are shown in Figure 4. The VIP values of age were 3.4491(>1) and it was the largest among the 13 risk factors. The correlation coefficient of age group was > 0. It showed that age was the key risk factor of severity of AEs caused by XYP.

### 3.3 VIP analysis of herb-drug combination in the first age group (0-6 years old)

In the first age group (0-6 years old), the VIP value of XYP alone was 1.4397 and the correlation coefficient was less than 0. It indicates a negative impact on the severity of AEs and tended to have general AEs.

The correlation coefficient of RB, CAZ and AH combination were more than 0. They indicate positive impact on the severity of AEs and tended to have Severe AEs. The influence of XYP-RB combination is greater than that of XYP-CAZ combination and greater than that of XYP-AH combination. Detailed information is shown in Table 2.

### Table 2 VIP value and correlation coefficient of the severity of AEs (in different age stage)
Note: The color depth shows the influence of each factor in this stage. The green flag indicates that the correlation coefficient < 0, and this factor had a negative impact on the severity of AEs and tended to have general AEs. The red flag indicates that the correlation coefficient > 0, and this factor had an active impact on the severity of AEs and tended to have severe AE.

### 3.4 VIP analysis of herb-drug combination in the second age group (7-17 years old)

In the second age group (7-17 years old), the VIP values of XYP-FOX, AZM combination were 1.14 and 1.48 respectively, and the correlation coefficient were less than 0. It had a negative impact on the severity of AEs and tended to have general AEs. The VIP values of XYP-CSP and -AMC combination were 1.5235 and 1.7724 respectively, and the correlation coefficient was > 0. Under the influence of these factors, it tended to increase the severity of AEs and the influence of XYP-CSP combination is greater than that of XYP-AMC combination.

### 3.5 VIP analysis of herb-drug combination in the third age group (18-40 years old)

In the third age group (18-40 years), the correlation coefficient of XYP alone and XYP-FOX combination were less than 0. It had a negative effect on the severity of AEs and tended to have general AEs. The VIP values of XYP-RB and XYP-DA were 1.7204 and 1.2954 respectively, and the correlation coefficient was > 0. Under the influence of these factors, it tended to increase the severity of AEs and the influence of XYP-RB combination is greater than that of XYP-DA combination.

### 3.6 VIP analysis of herb-drug combination in the fourth age group (41-65 years old)

The VIP value of XYP alone was 1.786 and the correlation coefficient was less than 0, indicating this factor had a negative impact on the severity of AEs and tended to have general AEs. The VIP values of XYP-CTR, PS, FOX combination were less than 0. It had a negative effect on the severity of AEs and tended to have general AEs. The VIP values of XYP-CTR, PS, FOX combination were 0.7886 and 0.1073 respectively, and the correlation coefficient was > 0. Under the influence of these factors, it tended to increase the severity of AEs and the influence of XYP-CTR combination is greater than that of XYP-PS combination and greater than that of XYP-FOX combination.

### 3.7 VIP analysis of herb-drug combination in the fifth age group (> 65 years old)

The contribution of combination drugs to the severity of AEs was analyzed in cases in the fifth age group (> 65 years old). The correlation coefficient of XYP-RB, DA, AMC combination was less than 0, indicating this factor had a negative impact on the severity of AEs and tended to have general AEs. The VIP values of XYP-RB, DA, AMC combination were less than 0. It had a negative effect on the severity of AEs. The VIP values of XYP-RB, DA, AMC combination were 0.7886 and 0.1073 respectively, and the correlation coefficient was > 0. Under the influence of these factors, it tended to increase the severity of AEs. The two groups had the same impact on the severity of AEs.

### 4 Discussion

#### 4.1 Introducing VIP method into clinical medical statistics
Multivariate data analysis is often applied to the analysis of large data sets in analytical chemistry, medical statistics\textsuperscript{[14]}, pharmaceutical engineering\textsuperscript{[15–18]}, food science\textsuperscript{[19]}, biology\textsuperscript{[20]}, psychology, economics, sensory science and industrial processes\textsuperscript{[21, 22]}. However, the VIP analysis method was rarely used in the analysis of clinical risk factors. In practical applications, the descending order of VIP values was often used to select variables or evaluate the importance of independent variables. The VIP filtering has been the preferred method in most variable selection scenarios because of its speed and efficiency. The VIP is simple and the results are interpretable, which accounts for influence of input variables for both explaining X and Y. The parameter selection/elimination of VIP is based on statistical tests and the recommended variables are given\textsuperscript{[23]}.

VIP scores are useful in understanding X space predictor variables that best explain Y variance. VIP method selects those X variables that contribute most to the underlying variation in the X variables\textsuperscript{[24]}. So, we highly advise to use a variable selection method like VIP to evaluate the risk factors affecting outcome indicators in clinical studies\textsuperscript{[25]}.

### 4.2 Age May Be A Key Factor Of Combination's Safety

According to the annual report of national adverse drug reaction monitoring (2021), 31.2% AEs patients age was over 65 years old in China\textsuperscript{[418]}. Some studies have found that age is a common risk factor of AEs\textsuperscript{[27]}. Based on the clinical surveillance cases of clinical safety in 296 200 cases, age is also the related risk factor of TCM injection\textsuperscript{[28]}.

A novel method (VIP analysis) was used for analyzing key factors contributing to the severity of AEs with different influence. In the included age and 12 herb-drug combination group, age is the only key factor of Severe AEs. Immune cells have different characteristics at different stages, for example, antigen-naïve CD8\textsuperscript{+} T cells exhibit marked proliferative dysfunction in advanced age\textsuperscript{[29]}. It is necessary to conduct targeted clinical safety analysis of different drugs according to the metabolic and immune characteristics of age groups. The XYP-RB combination was not only a risk factor for the severity of AEs, but also showed different effects in different age groups\textsuperscript{[5, 6]}. Therefore, age as a key factor of combination's AEs should be get further attention.

### 4.3 Aes Of Xyp-rb Combination Tended To Be Severe

Patients in both age groups (0–6 and 18–40 years old), XYP-RB combination is a top factor of increasing AEs severity. 270 XYP AEs is mainly concentrated in patients under the age of 14, especially infants under the age of 4, accounting for 67.1\%\textsuperscript{[30]} in Fujian Province. XYP is widely used in pediatric diseases, including pediatric upper respiratory tract infection\textsuperscript{[30]}, pediatric viral pneumonia\textsuperscript{[32]} and so on. Children, especially infants, are not fully developed. They are relatively sensitive to drugs and are more likely to develop AEs\textsuperscript{[33]}. 0–6 years old patients should carry out the targeted pharmacokinetic tests, not simply using dosage converted from adult.

The aged have more complex effects of drug combination, because the metabolism slow down and different basic diseases. Meanwhile, in patients over 65 years old, the contribution of XYP-RB combination tends to lighten the severity of AEs. There may be new interactions of action target or metabolism, or other unknown factors to reduce AEs. Fasudil is a commonly used drug for improving cerebral microcirculation and promoting nerve regeneration. At the same time, it is also a ROCK inhibitor\textsuperscript{[34]}. RhoA/ROCK signaling pathway is a related pathway regulating vascular permeability. Blocking the activation of RhoA/ROCK signaling pathway can inhibit the occurrence of anaphylactoid reaction\textsuperscript{[35]}. People over 65 years old are prone to have cerebrovascular diseases. In clinical application, drug combinations may inhibit the severity of AEs.

### 4.4 Possible Aes Mechanism Of Xyp-rb Combination

It is necessary to carry out injection safety tests including histamine substances and allergic reactions. Type I allergic reaction can be probably excluded. The clinical symptoms of anaphylactoid reaction are similar with type I anaphylactic reaction. Anaphylactoid reaction can appear at the first contact without sensitization process. Foreign substances directly stimulate immune cells to cause the release of inflammatory mediators. The mechanism is mainly characterized by the change of vascular permeability\textsuperscript{[36]}. It was reported in the adverse drug reaction information circular (issue 48) issued by the State Drug Administration that XYP adverse events / AEs involved skin and its accessories damage, accounting for about 16.4\%\textsuperscript{[37]} and 96.3\% AEs occurred on the first medication, especially within 30min (accounting for 43\%)\textsuperscript{[31]}. 46.7\%AEs induced by RB occurred within 30 min\textsuperscript{[38]}. More than 34.9\% of AEs are skin rash and skin mucosal edema\textsuperscript{[39, 40]}. Slowing down the speed of intravenous drip and stopping the drug can make the patient return to normal\textsuperscript{[41]}. XYP and RB basically conform to the characteristics of anaphylactic reaction.

The superposition of pharmacodynamic substances is the superposition of multiple components at the same target. It refers to the pharmacological effects produced by the superposition of the concentration of each compound\textsuperscript{[42]}. Therefore, we consider that the of XYP-RB combination may increase the actual dose acting on the target, enhance the activation of the target, or combination active different targets in related AEs pathway.

Cytochrome P450 is the main enzyme system of drug metabolism and a key targets of drug AEs. XYP regulates the combination metabolism by inhibiting P450 enzymes. For example, XYP significantly increases all pharmacokinetic parameters of Glibenclamide by inhibiting CYP3A4\textsuperscript{[43]}.
Studies have found that Reduning injection, a TCM injection, inhibits the gene expression of CYP1A2, CYP2A6 and CYP2B6. It changes the pharmacokinetics of RB, so greatly increases RB plasma concentration in the liver and initiates the side effects \[44\]. XYP as TCM injections for clearing away heat and detoxication are similar with Reduning injection. Whether XYP-RB combination have similar effects and why have different effect in different age groups need to be further explored.

4.5 Corresponding Countermeasures

(1) Standardize the route of administration

XYP alone tends to have general AEs, suggesting that XYP alone may have good safety. XYP-RB combination is more effective in the treatment of severe hand, foot and mouth disease \[45\]. Therefore, how to balance and improve the curative effect should be focused on the ensuring safety. Basic Principles for Clinical Use of Traditional Chinese Medicine Injections specify that traditional Chinese medicine injections should be used alone. If they really need to be used with other drugs, the interval between two doses should be carefully considered. It is recommended to flush the infusion tube during dressing change.

It was found that there were non-standard drug delivery routes such as ophthalmic administration and subcutaneous injection, in the process of sorting out the spontaneous reporting system. Different routes of administration have different preparation requirements, which may bring unknown risks. It is emphasized that standardizing drug use according to the instructions can avoid unnecessary risks and is a feasible way to ensure drug safety.

(2) Strengthening mechanism research

The TCM and Western medicine is a common clinical combination, but how to reasonably evaluate the clinical safety has always been a dilemma. VIP analysis showed that the XYP-RB combination had a significant contribution to the severity of XYP AEs. We can refer to the clinical safety evaluation method “Feature target correlation method” to extract the symptom characteristics of AEs and correlate the target mechanism. It helps to avoid the same kind of drugs combination and improve the drug safety \[46\].

4.6 Limitations

There are several limitations in this study. First, we were only able to access XYP’s AE-related information in the NADRMIS database from 2004 to 2020 and twelve commonly used clinical combinations were analyzed. These findings do not reflect the entire usage history and culture of XYP but rather a snapshot of clinical use. Second, AE reports may be influenced by factors not included in NADRMIS, such as genetic characteristics cannot be addressed in our analyses. Third, this study only analyzes the phenomenon, the analytical ability of this method to more factors and the mechanism behind need further verification. Further studies should make more analyses to illustrate the Severe AEs were attributed to combination rather than single drug/herb.

5. Conclusions

VIP scores are useful in evaluating the risk factors affecting outcome indicators in clinical studies. Age may be a key factor on the severity of XYP’s AEs and different age patients have different sensitivity to different drugs combination. Combined with the previous researches, XYP-RB combination tends to aggravate AEs. It is recommended that clinical practitioners should pay attention to the metabolic characteristics of different age groups. It is safer to use XYP alone and strictly implement standardized operations such as medication interval and flushing.

Abbreviations

AEs: adverse events; AH: ambroxol; AMC: amoxicillin sodium and clavulanate potassium; AZM: azithromycin; CAZ: ceftazidime; CEF: cefuroxime; CSP: cefazolin sodium pentahydrate; Coeff: correlation coefficient; CTR: ceftriaxone; DA: clindamycin; FOX: cefoxitin sodium; LEVH: levofloxacin hydrochloride; NADRMIS: National Adverse Drug Reaction Monitoring Information System; PS: penicillin sodium; RB: ribavirin; VIP: variable importance for projection; XYP: Xiyanping injection.

Declarations

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Not applicable.

Contributions of authors
RZ, ZC and HS conceived and designed the research; RZ, ZC, HC collected the data; ZC, CZ analysis the data; RZ, ZC and ZG wrote this manuscript; CZ, HC and HS revised the manuscript. All authors read and approved the final manuscript.

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**Availability of data and materials**

All data used in the presented study can get from the corresponding author upon request.

**Ethics approval and consent to participate**

This study protocol was approved by corresponding Research Ethics Committee(s) in China and followed the guidelines in the Declaration of Helsinki and ICH Good Clinical Practice. Research ethics committees that reviewed and granted approved to this study is Ethics Committee of Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine (No. 2022DZMEC-036-01).

**Consent for publication**

All the authors have agreed that the manuscript published in Chinese Medicine.

**Competing interests**

The authors declare that they have no conflicts of interest.

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Figures

Figure 1
Top three sales of TCM for respiratory system in 2019

![Figure 1](image1.png)

Figure 2
the schematic design of VIP method

![Figure 2](image2.png)
AEs of XYP in NADR MIS (2004-2020), n=38018

Recorded excluded (n=9419)
- Removed duplicated (n=5070)
- Missing AEs or age (n=11)
- Other combination (n=2897)
- Multi drug combination (n=1441)

Cases involving XYP alone and 12 XYP-drug combination, n=28599
(General AEs, n=27037; Severe AEs, n=1562)

Figure 3
Flow diagram for analysis of AEs

Figure 4
VIP value and correlation coefficient of the severity of AEs (including age and herb-drug combination)