보건학석사 학위논문

Epidemiologic characteristics of anaphylaxis reports after COVID-19 vaccination in Seoul, Korea

대한민국 코로나19 예방접종 후 아나필락시스의 역학적 특성 연구

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서울대학교 대학원

보건학과 및 보건학 전공

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대한민국 코로나19 예방접종 후 아나필락시스의 역학적 특성 연구

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연구배경

2022년 2월 26일은 대한민국에서 코로나19 예방접종을 시행한지 1년이 되는 날이다. 대한민국의 코로나19 예방접종 시행현황은 국가권고 3차 접종 완료자가 28,171,739명으로 전체 인구대비 55.4%이다. 코로나19 예방접종 후 이상반응 신고자는 총 460,007건이었다. 그 중 단시간에 생명을 위협할 수 있는 치명적인 특성으로 인해 특별관심이상반응으로 지정되어 집중 감시 중인 아나필락시스 의심 신고는 총 1,934건으로, 접종 10만 건당 1.63건이다. 영국 1.15건, 독일 0.36건, 일본 1.52건에 비해 대한민국의 발생률(incidence rate)은 비교적 높은 편이다. 문제는 아나필락시스가 Vaccine hesitancy에 영향을 미치고 있다는 것이다. 그래서 대한민국에서 코로나19 예방 접종을 한 지 1년이 되는 현시점에서 아나필락시스 의심 신고의 역학적 특성을 알아보고, 진단 적합성 판정도구인 Brighton Collaboration Case Definition의 타당도를 측정하여 아나필락시스로 인과성을 인정받은 사례에 대해 재검토를 하고자 한다.

연구방법

질병관리청 ‘질병보건통합관리시스템’에 2021. 2. 26.부터 2022. 2. 26까지 코로나19 예방접종 후 이상반응 신고 중 ‘아나필락시스’ 또는 ‘아나필라시스 양반응’ 으로 신고한 사례의 인구학적 특성과 임상증상 특성을 분석했다. 또 이를 바탕으로 예방접종 후 아나필락시스 발생과 관련이 있는 위험요인 (성별, 나이, 접종한 백신, 이전 약물/음식에 대한 알러지 반응 경험의 유무)을 선별하여 상관관계를 다중회귀분석을 통해 알아보았다. 또한 진단적합성 평가를 받은 사례의 민감도와 특이도를 계산하여, 타당도를 측정했다. 이를 통해 코로나19 예방접종을 시행하는 다른 국가들에 비해 높은 아나필락시스 의심 신고율을 보이는 원인을 고찰하였다.

연구결과

대한민국 코로나19 예방접종 후 아나필락시스 의심 신고는 총 1,934건이었고 이 중 Brighton Collaboration Case Definition을 통해 진단 적합성 평가 및 코로나19 백신과 인과성 평가에서 인정받은 사례는 841건이었다. 접종 10만 건당 1.63건의 신고와 0.71건이 인과성을 인정받았다. 동일기간 서울특별시 코로나19 예방접종 후 아나필락시스 의심 신고는 총 534건이었고, 이 중 Brighton Collaboration Case Definition을 통해 진단 적합성 평가 및 코로나19 백신과 인과성 평가에서 인정받은 사례는 145건이었다. 접종 10만 건당 0.44건의 신고와 0.12건이 인과성을 인정받았다.

서울특별시 코로나19 예방접종 후 아나필락시스 의심사례 신고(총 534건)의 인구학적 특성은 여성이 71.7%, 20-29세가 26.8%, 화이자 백신 피접종자가 73.8%, 접종 이전 약물 또는 음식에 알러지

반응이 없었다고 대답한 피접종자가 77.5%로 차지했다.

서울특별시 코로나19 예방접종 후 아나필락시스에 대해 인과성 인정 사례에서 임상증상은 '갑자기'와 '빠르게' 조건을 충족하면서 호흡기계(72.9%), 심혈관계(51.5%), 피부점막 증상(32.9%), 위장관계(25.3%) 순으로 많이 나타났다. (1건은 빠르게 조건을 미충족했지만, delayed anaphylaxis symptom으로 인과성을 인정받았다.) 접종 후 증상 발생까지 소요 시간으로는 15분미만이 가장 많았다. 실험실 검사를 시행한 사례는 없었으며, 치료방법으로는 에피네프린(64.1%), 항히스타민제(49.7%), 부신피질스테로이드(41.4%), 산소투여(20.0%) 순으로 많았다.

코로나19 예방접종 후 아나필락시스 의심사례 신고율 증가의 원인을 알아보기 위해 신고사례들을 대상으로 분석했으며, 이와 관련이 있을 것으로 추정되는 위험요인을 선별하였다. 피접종자의 성별, 나이, 접종한 백신의 종류, 이전 약물 또는 음식에 알러지 반응의 경험 유무 4가지로 설정하고, 접종 후 아나필락시스 발생과의 상관관계를 알아보았다.

서울특별시 전체 코로나19 예방접종 후 아나필락시스 의심사례 신고는 총 534건이었으며, 그 중 코로나19 예방접종과 인과성이 인정된 '아나필락시스'집단은 145건, '비(非)아나필락시스'집단은 340건이었다. 그 중 인과성 결과가 미보고된 11건은 제외하였다. '아나필락시스'집단에 대한 각 위험요인들이 차지하는 분율은 다음과 같다. 성별의 경우 남성 26.9%, 여성 73.1% 이었다. 나이의 경우 중위값은 34세(표준편차 : ±15.55)이었다. 접종한 백신의 종류에 따라서는 화이자 75.2%, 아스트라제네카와 모더나가 8.9%, 얀센이

7.0%를 차지했다. 이전 약물 또는 음식에 알러지 반응의 경험 유무는 '있음'이 42.8%, '없음'이 57.2%를 차지했다. 접종부터 증상이 나타나기까지 평균 82.82분(표준오차 : ±18.47)이 걸렸다. 앞서 선정한 위험요인들로 카이제곱검정을 통해 Odds ratio를 계산했고, 그 결과 백신 종류에 따라 차이가 있었으며, 이전 알러지 반응 경험이 있었던 피접종자에서 Odds ratio가 2.78로 확인되었다.

이전 연구결과와 달리, 증가된 코로나19 예방접종 후 아나필락시스 의심 사례 발생률에 진단적합성과 인과성 평가에 사용되는 도구가 영향을 미쳤을 가능성을 확인하기 위해, Brighton Collaboration Case Definition의 타당도를 측정했다. 서울특별시 코로나19 예방접종 후 아나필락시스 의심 신고 자료와 그에 대한 진단적합성 평가결과를 각각 예측값과 진단결과로 두고 분석했다. 대상 사례는 코로나19 예방접종 후 아나필락시스 신고로 총 534건이었으며, 그 중 인과성 결과가 미보고된 11건이 제외되어 총 523건이었다. 분석 결과, 민감도 26%, 특이도 33% 이었고, ROC curve를 그려 구한 AUC의 면적은 0.73이었다. Muller가 제안한 기준에 따르면 대한민국에서 Brighton Collaboration Case Definition의 타당도는 $0.7 \leq AUC < 0.8$에 해당하므로 'Fair'이다.

결론

대한민국에서 진행된 이전 예방접종 관련 아나필락시스 연구 결과와 차이점은 2가지이다.

첫 번째, 예방접종 후 아나필락시스 발생률과 인과성 인정 사례 수에 차이가 있다. 코로나19 예방접종 이전 대한민국의 예방접종 관련 아나필락시스 발생은 매우 적게 보고되었는데, 각 연도별 백만

건당 발생률은 2005년 0.090건, 2012년에 0.079건, 2013년 0.071건, 2015년에 0.188건, 2016년에 0.036건 이었다. 인과성을 인정받은 사례는 2001년부터 2016년까지 총 13건이었다. 그러나 코로나19 예방접종 후에는 접종 10만 건당 1.63건의 신고와 0.71건이 인과성을 인정받았다. 코로나19 예방접종 이전과 이후 예방접종 관련 아나필락시스 의심 신고율과 인과성 인정 사례 모두 차이가 있으며, 코로나19 예방접종에서 증가했다.

두 번째, 예방접종 후 발생한 아나필락시스의 주요 임상 증상에 차이가 있다. 이전 아나필락시스에 대한 역학연구 자료에 따르면, 약물에 의한 아나필락시스의 일반적 임상 증상으로는 가려움증, 두드러기 등 피부점막 증상이 80-90%로 주를 이루고, 호흡기계 증상(70%), 소화기계 증상(30-45%), 심혈관계 증상(10-48%), 신경계 증상(10-15%) 순으로 나타났다. 반면 이 연구를 통해 확인된 코로나19 예방접종 후 아나필락시스로 인과성이 인정된 사례들의 임상적 특징은 호흡기계(72.9%), 심혈관계(51.5%), 피부점막 증상(32.9%), 위장관계(25.3%) 순으로 많이 나타났다.

대한민국 코로나19 예방접종 후 아나필락시스 의심 신고 및 인과성 인정 사례의 인구학적 특징과 임상증상 특징은 기존에 진행되었던 아나필락시스 관련 연구와 차이가 있었다. 진단 적합성을 평가하는 도구인 Brighton Collaboration Case Definition의 타당도가 확인됨에 따라, 높은 아나필락시스 의심 신고율에 대해서는 다른 원인을 알아볼 필요가 있겠다. 이 연구를 통해 코로나19 예방접종 후 아나필락시스에 대한 국민의 불안을 해소하여, 코로나19 백신뿐만 아니라 다른 Vaccine Preventable Disease에서도

Vaccine hesitancy가 줄어드는데 기여하길 바란다.

주요어 : 코로나19 예방접종, 예방접종과 관련된 아나필락시스, 아나필락시스, 예방접종 후 이상반응, 아나필락시스의 역학적 특징
학 번 : 2019-27596

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Chapter 1. Introduction

1.1 Current status of COVID-19 vaccination in Korea

February 26, 2022 was the one-year of the start of the COVID-19 vaccination campaign in Korea. By February 26, 2022. Those who have completed 3rd vaccination following recommendation by the Korea Advisory Committee on Immunization Practice(KACIP) was 28,171,739, 55.4% of the total population in Korea. The vaccination completion rate was 86.4% compared to the adult population 18 years of age or older. According to the weekly report 'Analysis of adverse reactions after COVID-19 vaccination, 52th'[28] A total of 460,007 adverse events were reported. And 1,934 cases of suspected anaphylaxis are reported after COVID-19 vaccination, it is 1.63 cases per 100,000 doses and it accounts for 0.42% of all adverse evnets reports. In other countries, for example, 1.15 cases in Untied Kingdom, 0.36 cases in Germany, 1.52 cases in Japan per 100,000 doses. Compared to other countries, the incident rate of anaphylaxis after COVID-19 vaccination is relatively high in Korea. Confirmed cases of report suspected anaphylaxis were total of 841 (22.2.26.), account for 43.49% which meets the diagnostic criteria for anaphylaxis and has been confirmed the causality, including COVID-19 vaccination and temporal probability.

One of adverse events after vaccination is anaphylaxis (including

allergic reaction), which is an acute, potential life-threatening systemic allergic reaction that may have a wide range of clinical manifestations. So the KACIP set anaphylaxis as Adverse Events of Special Interest(AESI) up to monitor recipients closely.

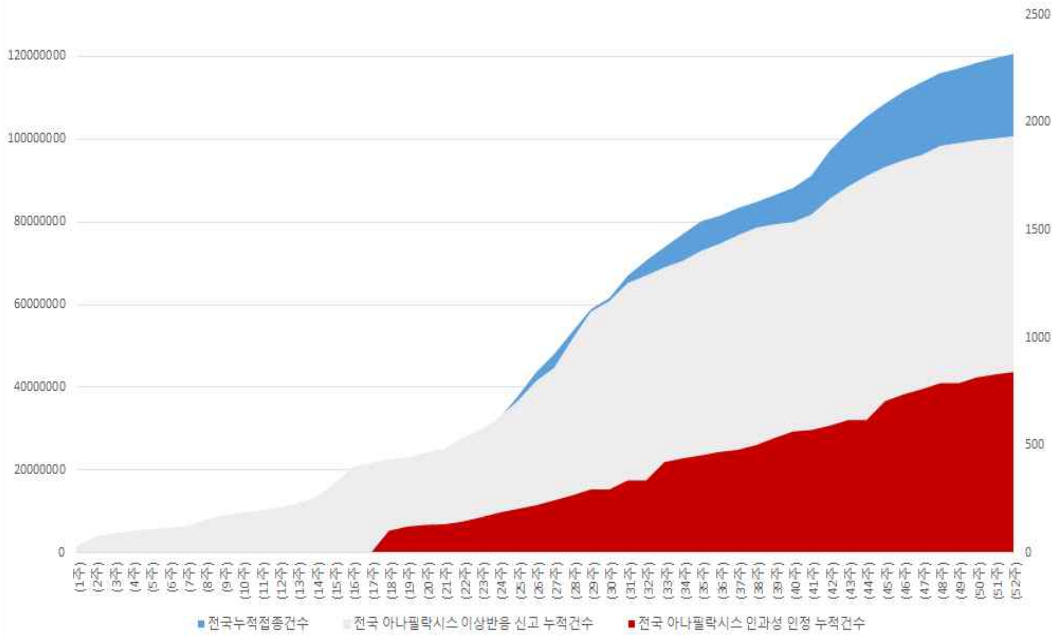

Figure 1. Cumulative graph of vaccination population and reported suspected anaphylaxis cases and confirmed anaphylaxis cases after COVID-19 vaccination in Korea (values represent case)

- Cumulative COVID-19 vaccination population in Korea
- Cumulative cases of reported suspected anaphylaxis cases after COVID-19 vaccination in Korea
- Cumulative cases of admitted anaphylaxis cases after COVID-19 vaccination in Korea

1.2 Overview of Anaphylaxis

'Anaphylaxis is an acute, potential life-threatening systemic allergic reaction that may have a wide range of clinical manifestations.

Severe anaphylaxis may include damage to the airways and respiratory or circulatory symptoms, and may be accompanied by typical skin symptoms or shock symptoms.[1]" defines The World Allergy Organ, WAO.

Anaphylaxis can be suspected when all three of the following symptoms are present: (1) 'sudden' onset and 'rapid' progression of symptoms (2) Airway and/or Respiratory and/or Cardiovascular problems, (3) Cutaneous or Mucosal changes(itching, redness, urticaria, angioedema). But, Cutaneous or mucosal changes alone are not indicative of an anaphylactic reaction, only bronchospasm or hypotension may occur without cutaneous or mucous membrane changes. Due to the unpredictable characters of the anaphylactic reaction, it is impossible to define a specific period of time that should be observed. Because immediate treatment is mainly required, stay at the vaccination centers for at least 15 minutes after vaccination and observe whether anaphylaxis occurs. Before vaccination, when a recipient has the past history of allergic reaction related other triggers (such as drugs, foods, injection, exercising, venom etc.) should stay at the vaccination center for at least 30 minutes after vaccination. The KACIP also recommends as same in the 'Adverse events management guidelines after COVID-19 vaccination'.

Even if the early phase of anaphylaxis symptoms are resolved, delayed reactions occur in 1-20% of anaphylaxis patients. It usually appears within 8 hours after the first symptom onset, but cases have been reported with a delay of up to 72 hours. Therefore, it is necessary to check the time elapsed from exposure to the triggers until clinical symptoms appear and do the clinical diagnosis as a anaphylaxis in very important. Investigate everything that the

recipient has exposed several hours before the onset of symptoms, for examples, drugs, drinks, acute infectious disease, stress especially the past history of allergic reaction. Symptoms are to be differentiated from anaphylaxis including asthma, anxiety disorder, panic disorder, vasovagal syncope, and acute coronary syndrome.

According to the Roh's study[49], there were 13 cases of vaccine-related anaphylaxis in Korea during 2001-2016. In study, The median age was 9 years old (range 1 month to 59 years). The incidence rates of vaccine-related anaphylaxis per million dose was 0.090 in 2005, 0.079 in 2012, 0.071 in 2013, 0.188 in 2015, 0.036 in 2016. Reported vaccinations were influenza (3/13, 23.1%), measles-mumps-rubella vaccine (MMR; 2/13, 15.4%), inactivated Japanese encephalitis vaccine(JEV)alone (2/13, 15.4%), JEV and tetanus-diphtheria-acellular pertussis vaccine(Tdap) together (2/13, 15.4%), Bacille Calmette-Guerin vaccine(BCG) intradermal type (1/13, 7.7%) and hepatitis B vaccine (HBV; 1/13, 7.7%). Compared to other countries, in the US, vaccine-induced anaphylaxis was rare at 1.31 per million doses across all ages during 2009-2011. In Germany, it is estimated at 6.8 cases per year.[49]

1.3 Problems with anaphylaxis in COVID-19 vaccination

The symptoms of anaphylaxis show different reactions to the same cause respectively, and appear in different ways even in same person. Due to the various symptoms and signs of anaphylaxis, it is difficult to measure the exact prevalence of anaphylaxis, and the diagnosis rate tends to be lower than the actual rate.[25]

Because the severity of the symptoms varies and it is difficult to diagnose, the KACIP set anaphylaxis as Adverse Events of Special Interest(AESI) up to monitor recipients closely and evaluated both the diagnostic eligibility and causality.

For judging cases which is reported as anaphylaxis after COVID-19 vaccination, there are 2 steps, (1) Brighton Collaboration case definition is a criteria for diagnostic eligibility (2) the 5 steps of causality evaluation suggested by the WHO are being applied for the causality with COVID-19 vaccine.

The evaluation process is that the recipient who has had an adverse events after the COVID-19 vaccination visits a medical center for treatment and then the medical center (or medical doctor) reports as suspected anaphylaxis with filling out the basic survey about anaphylaxis. After that, at the public health center where the medical institution is located, do the Interview with the recipient and fill out the rest of the basic survey. A local government where belongs to the health care center, evaluates the eligibility of anaphylaxis by BCCD. Referring to all, Korea Center for Disease Control and prevention Agency(below 'KDCA') evaluates the causality as final. The final discussion result is delivered to the recipient who has been reported as suspected of anaphylaxis.

According to the Korean COVID-19 vaccination enforcement policy, a recipient who is evaluated Level 1, 2, 3, 4 is classified as a contradiction of additional vaccine dose on the same type. (Vaccination on other platforms can be considered after consulting with medical doctors.) If someone who is vaccinated type of Viral vector, there is no problem to do cross vaccination to mRNA, the opposite could be a problem.

There are two types of viral vector vaccines available in Korea:

AstraZeneca and Janssen. In the case of the AstraZeneca vaccine, there is an age limitation for people below 60. Due to the Korean vaccination policy to mainly vaccinate mRNA type to the public, very few medical institutions are able to vaccinate the Janssen. As a countermeasure to this problem, Novabax vaccine has approved additionally, a different type of platforms before, and started vaccination to the public in Korea on February 14, 2022. However, due to the short vaccination period, monitoring data of adverse events is insufficient. Lack of evidence for safe vaccination and uncertainty over the occurrence of adverse events can not only cause anxiety among the people who have to be vaccinated, but also act as obstacles to the governments and the department of public health's plan to quell the large-scale epidemic of COVID-19 through immunization.

In addition, the risk of anaphylaxis is acting as a major factor in Vaccine Hesitancy. According to other studies, including the National Institute of Health (NIH), that infection prevention effects continue to decrease over time after COVID-19 vaccination[2)], KDCA also recommends a tertiary vaccination of the COVID-19 vaccine. At a time when a large-scale fourth vaccination is planned soon, it is necessary to closely examine about the suspected anaphylaxis cases reported as adverse events after COVID-19 vaccination.

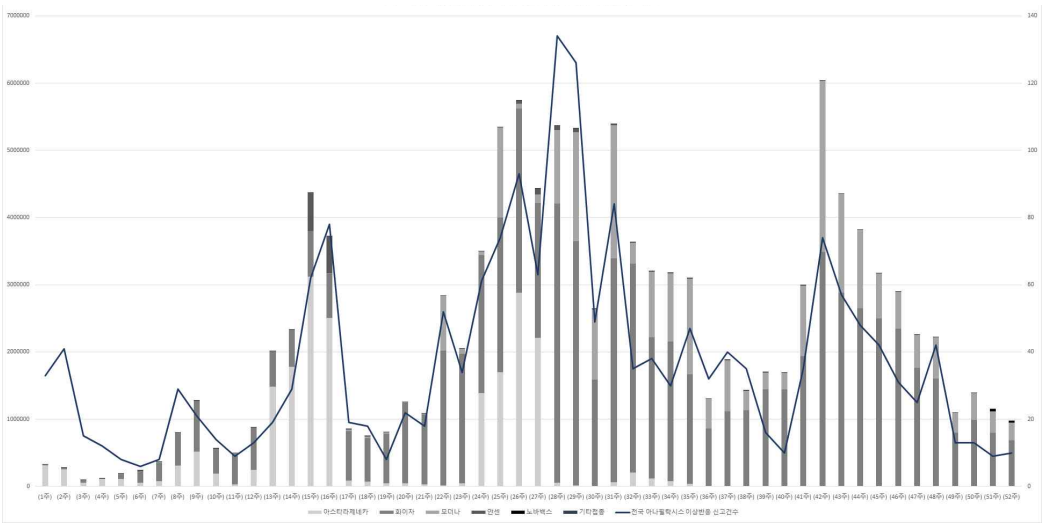

Figure 2. Weekly report of COVID-19 vaccination, suspected anaphylaxis cases in Korea (values represent case)

■ Report of suspected anaphylaxis cases after COVID-19 vaccination in Korea

1.4 Research Objective

The demographic characteristics and clinical symptoms of suspected anaphylaxis reports after COVID-19 vaccination in Korea are analyzed and compared with the results of previous studies on the incidence of anaphylaxis related to vaccines. The epidemiological characteristics of anaphylaxis known in previous studies and newly discovered risk factors through analysis of suspected cases of anaphylaxis after COVID-19 vaccination are examined, and the correlation with the incidence of anaphylaxis is investigated.

The sensitivity and specificity of Brighton Collaboration Case Definition in Korea, a criteria of diagnostic eligibility for Anaphylaxis after vaccination, are measured. Based on the result, the validity of BCCD is examined to prevent the incorrect classification such the

recipient in the high-risk group which is needed vaccination as COVID-19 vaccination contradiction, ultimately. Furthermore, not only for the COVID-19 vaccination, but for the other vaccination campaign, this study is used to prevent anaphylaxis and could be the evidence which is necessary for management of recurrence and prognosis and education to the public.

Chapter 2. Materials and Methods

2.1 Research Plan

1. Application of descriptive statistics analysis to the report of suspected anaphylaxis after COVID-19 vaccination in Korea and Seoul
2. Examination of the correlation between anaphylaxis and risk factors in Seoul
3. Evaluation of the validity of criteria for diagnostic eligibility at anaphylaxis in COVID-19 vaccination in Seoul

2.2 Collection of data and characteristics of data

1. Data of report suspected anaphylaxis after COVID-19 vaccination in Korea

Adverse events after the COVID-19 vaccination reported on the vaccination management system of KDCA which is the national surveillance for AEFI or AESI by the reports of medical doctors or medical centers were analyzed. Data collecting period is from February 26. 2021. to February 26, 2022. It was a year since the COVID-19 vaccination began in Korea. According to KDCA's COVID-19 vaccination management manual, the case classification criteria for anaphylaxis is the report as 'Anaphylaxis' or 'Suspected anaphylaxis' to KDCA system. A total of 1,934 cases meet the criteria. Collection material is a public data posted on the website (https://ncv.kdca.go.kr) of the KDCA's COVID-19 vaccine and vaccination operated by the KDCA were used.

The characteristics of the 1,934 cases were analyzed by sex, age, the past history of allergic reaction related drugs/food, symptom onset, treatment, severity, current status after treatment. Those variables are classified as demographic information. Among the collected data, those who canceled the report of suspected anaphylaxis within the same period or those who were reported for other diagnosis were excluded. Those who were reported as duplicates in the collection data were not identified during the review, because in korea, when a recipient is reported as a suspected anaphylaxis, it is impossible to vaccinate the same type / the same platform and the recipient is registered 'Not vaccinated' on the KDCA management system.

2. Data of report suspected anaphylaxis after COVID-19 vaccination in Seoul

Data collecting period and the case classification criteria were the

same as above. The report as 'Anaphylaxis' or 'Suspected anaphylaxis' to KDCA system(is.cdc.go.kr)' after COVID-19 vaccination. 72,171 cases were reported as adverse events after the COVID-19 vaccination, but those cases were included all report who was registered address 'Seoul'. In case of anaphylaxis, according to KDCA's COVID-19 vaccination management manual, since the city and district in charge of the reporting agency were the subject of the investigation. It was reclassified through where the location of the reporting agency was 'Seoul', and there were 534 cases in total. Among them, 145 cases were confirmed the eligibility by the BCCD(Brighton Collaboration Case Definition level 1,2,3) for the diagnosis and the causality from KACIP. In the report data of Seoul, those who canceled the report or reported as other diseases were excluded, and there were no duplicates.

The characteristics of the 534 cases were analyzed by sex, age, the past history of allergic reaction related drugs/food, symptom onset, treatment, severity, current status after treatment. Those variables are classified as demographic information. And clinical symptom information of 534 cases was collected. The clinical symptom information was based on the basic survey of anaphylaxis and their clinical records which recipients submitted for evaluating the diagnostic eligibility and causality on vaccination. On the phase of clinical symptoms, the variables are Cutaneous/Mucosal, Cardiovascular, Respiratory, Gastrointestinal symptoms were collected in accordance to KDCA's anaphylaxis manual.

The basic survey of anaphylaxis are composed 10 questionnaire. From Q1 to Q5, questions about suspected anaphylaxis symptoms, which is filled by a medical institution which were reported suspected anaphylaxis cases. And then from Q6 to Q10, questions about the

recipient's current status and the past history, which was prepared through an interview with the recipient at the healthcare center where the reported medical center is located. But it was possible to report suspected anaphylaxis at other medical centers even if they did not provide treatments to the recipient. The data of the basis survey of anaphylaxis were reviewed by the medical records through using data source to check the facts of the report and add and supplement it.

3. The Validity of Diagnostic eligibility evaluation criteria of anaphylaxis

In Korea, Brighton Collaboration Case Definition (below BCCD) is a criteria for evaluating diagnostic eligibility of anaphylaxis after vaccination. There are two types of evaluation results for suspected anaphylaxis reporting cases. (1) The level is automatically determined as reported according to BCCD on KDCA management system. (2) The level is confirmed by local government through reviewing all materials about anaphylaxis report. In this study, this step is needed to examine differences between the two values determined in those 2 ways and the medical records of the cases. With this results, the steps for drawing the ROC curve and calculating the AUC was necessary in order to evaluate the validity of BCCD in Korea.

In BCCD of Anaphylaxis, departed as major symptoms or minor symptoms categories. There was no difference in scores of each categories, it was classified only as 'Yes (1)' and 'No (2)' according to the algorithm. The optimal score or cut point of confirmed level 1, 2, 3 on BCCD was meaningless, theses were excluded.

To draw the ROC curve, the variables were two results. The expected value was the level of determined automatically on the KDCA's management system. The test result was the conclusion level of assessed by BCCD with reviewed recipient's medical record.

The prior test was conducted by applying variables and making 3 groups to determine the subject of study.

Group ① : exclude level 4 from the test result

Group ② : include level 4 from the test result

Group ③ : the test result was only the medical records and including level 4. All the result represent case.

In Group ①, the prior test result was True-Positive:102, False-Negative:1, False-Positive:17, True-Negative:1, sensitivity:99%, specificity: 6%. Group ①'s condition was the exclusion of level 4 from the test result. A total of excluded cases were 413 of 534. Level 4 means 'insufficiency information to diagnosis' on the other hand, these cases still had possibility to get eligibility but suspended a decision because of insufficiency information. Therefore, these cases were not diagnosis 'anaphylaxis' certainly, all of them were excluded. Since the True-Negative was only 1 case, Group ① was judged to be inappropriate because the number was insufficient to judge the validity.

In Group ②, the prior test result was True-Positive:102, False-Negative:290, False-Positive:88, True-Negative:43, sensitivity:26%, specificity:33%. Group ②'s condition was the inclusion of level 4 from the test result as the False. It was the basis of COVID-19 vaccination policy in Korea, cases of level 4 means suspended eligibility, but their causalities were 'unlikely' in conclusion that means not 'True' but 'False'. Therefore, test result and the number of each part is sufficient, Group 2 was judged to be appropriate for this study.

In Group ③, the prior test result was True-Positive:36,

False-Negative:14, False-Positive:83, True-Negative:38, sensitivity:0.72, specificity:0.31. Group ③'s condition was that the medical record was only source of test result not based on BCCD assessment. But this condition had limitation, that the accuracy of medical center's diagnosis or department of causality assessment is confirmed, not the validity of BCCD. It was inappropriate for this study, so Group ③ was excluded.

There were some limitations during rechecking the medical records which was submitted by the recipients is that (1) differences in the tests by medical centers where every the recipient visit to treatment their symptoms. (2) Most of the records in medical centers were the first treatment before visiting, and most of the results were after treatment of epinephrine or antihistamine or both.

Because of limitations, detected records of vital sign (blood pressure, pulse rate, respiratory counts etc) were stable as usual. These couldn't meet the criteria of BCCD. Differences between assessment of diagnostic eligibility by BCCD and Diagnosis by medical center were inappropriate for this study. So the medical records were used as supplement sources.

2.3 Statistical Analysis

Microsoft® Excel® 2016 MSO(version 2201, 16.0.14827.20180) 32 beats, R version 4.0.5.(R foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis.

The data of the report of suspected anaphylaxis after COVID-19 in korea and seoul was conducted descriptive statistic and the conclusion represent case and proportion(%).

The variables for analysis with the risk factors were chosen by the

report of seoul. (sex, age groups, vaccine type, the past history of allergic reaction related to food/drugs) Each variables are compared to independent t-test. Age groups represented median age and standard deviation. Statistical significance was defined as a $p\text{-}value < 0.05$. PMR odds ratio of each variables were calculated by the chi-square test. Age groups and vaccine type which were confirmed statistical significance made a correction. And then multiple regression method was used to analyze the correlation to the incidence of anaphylaxis.

To examine the validity of BCCD, the sensitivity and the specificity were calculated. And the result was used by drawing ROC(Receiver Operating Characteristic) curve and calculate AUC(Area under the ROC curve) by using 'Epi'packages of R. The result of AUC was determined by applying the criteria of Muller(2005).[67)]

Chapter 3. Result

3.1 Demographic characters of report suspected anaphylaxis after COVID-19 vaccination in Korea

During the research period, a total of 1,934 cases were reported as anaphylaxis after COVID-19 vaccination in Korea.[35)] Of whom 595(30.8%) were men and 1339 (69.2%) were women and as per 100,000 doses, 1.01 cases were men and 2.24 cases were women. The median age was 39.98 years old (SD 16.04) (data was ended 2021.10.31., no KDCA announcement since then). Stratified the data

by the age groups into 10 years, getting older decreased the incidence trends except the group of below 19 years old. Those aged 20-29 years were 26.1% had the highest proportion of the report, 30-39 years (21.9%), 40-49 years (19.7%), 50-59 years (12.8%), 60-69 years (6.8%), 70-79 years(2.3%), below 19 years and 80-89 years (2.2%) were following. (At the time of the study, the population under the age of 12 was excluded because COVID-19 vaccination was not conducted in Korea.)

A total of 1,516 cases reported as suspected anaphylaxis after 1st dose had 78.4% of the entire reports. After 2nd dose were 322 cases(16.6%), 3rd dose were 96 cases(5.0%) were following.

In vaccine types, The Pfizer COVID-19 vaccine were 1,254 cases(64.8%, 1.72 cases per 100,000 doses) which had the largest proportion of the entire reports, and AstraZeneca COVID-19 vaccine 331 cases(17.1%, 1.63cases per 100,000 doses), Moderna COVID-19 vaccine 291 cases(15.0%, 1.22 cases per 100,000 doses), Janssen COVID-19 vaccine 54 cases(2.8%, 3.58 cases per 100,000 doses), Novavax COVID-19 vaccine 4 cases(0.3%, 6.64 cases per 100,000 doses) were following. (Table 1)

During the same period, 534(27.6%) out of 1,934 cases were reported as anaphylaxis after COVID-19 vaccination in Seoul. Of whom 151 (28.3%) were men, and 383(71.7%) were women. The median age was 34 years old(SD 15.55), Stratified the data by the age groups into 10 years, as the same of above, getting older decreased the incidence trends except the group of below 19 years old. Those aged 20-29 years were 26.8% had the highest proportion of the report, 30-39 years (24.3%), 40-49 years (21.7%), 50-59 years (11.4%), 60-69 years (7.1%), below 19 years (6.4%), 70-79 years(1.5%), 80-89 years (0.7%) were following. Compared to the

report of Korea(national), In 12-19 years, the 3.7 cases per 100,000 dose were doubled.

A total of 423 cases reported as suspected anaphylaxis after 1st dose had 79.2% of the entire reports. After 2nd dose were 90 cases(16.9%), 3rd dose were 21 cases(3.9%) were following.

In vaccine types, The Pfizer COVID-19 vaccine were 394 cases(73.8%) which had the largest proportion of the entire reports, and AstraZeneca COVID-19 vaccine 65 cases(12.2%), Moderna COVID-19 vaccine 53 cases(9.9%), Janssen COVID-19 vaccine 20 cases(3.8%), Novavax COVID-19 vaccine 2 cases(0.4%) were following.

During the same period, the confirmed cases were a total of 841 cases, 145 cases out of them were the reports of Seoul. In proportion, 17.2% of the entire cases. As per 100,000 doses, 0.71 cases in Korea, 0.12 cases in Seoul were confirmed as anaphylaxis after COVID-19 vaccination. These showed the same trends with the report, women than men, 20-29 years, after 1st dose, the Pfizer Bio-NTech COVID-19 vaccine had the largest proportion. (Table 2)

Table 1. The reports of adverse events after receipt of COVID-19 vaccines, by recipients' sex, age group, and type of vaccine : Korea, from February 26, 2021 to February 26, 2022 (n=460,007)

Variable	Vaccination dose	Sub-total	Suspected				Confirmed		
			Total (case)	%[a]	%[b]	Adverse events reported per 100,000	Total (case)	%[c]	Confirmed case per 100,000
Total	118,609,672	460,007	1,934	0.42	100.0	1.63	841	43.49	0.71
Sex									
Male	58,769,489	164,890	595	0.36	30.77	1.01	247	12.77	0.42
Female	59,840,183	295,117	1339	0.45	69.23	2.24	594	30.71	0.99
Age groups									
12-15	2,698,315	6,105	43	0.70	2.22	1.59			
16-17	1,707,532	6,384	45	0.70	2.33	2.64			
18	1,314,494	5,548	36	0.65	1.86	2.74			
19	1,183,607	5,066	75	1.50	3.88	6.34			
≤ 19	6,903,948	23,103	158	0.68	8.17	2.29	63	3.26	0.91
20-29	16,374,904	78,093	505	0.65	26.11	3.08	250	12.93	1.53
30-39	15,355,757	76,954	425	0.55	21.98	2.77	177	9.15	1.15
40-49	20,098,346	77,898	381	0.49	19.70	1.90	180	9.31	0.90
50-59	23,560,098	79,778	247	0.31	12.77	1.05	94	4.86	0.40
60-69	20,238,316	77,624	131	0.17	6.77	0.65	44	2.28	0.22
70-79	10,489,303	33,771	45	0.13	2.33	0.43	15	0.78	0.14
≥ 80	5,589,000	12,786	42	0.33	2.17	0.75	18	0.93	0.32
Vaccine dose									
1st dose	44,642,674	238,853	1,516	0.63	78.39	3.40	680	35.16	1.52
2nd dose	42,651,470	172741	322	0.19	16.65	0.75	127	6.57	0.30
3rd dose	31,303,714	48412	96	0.19	4.96	0.31	34	1.76	0.11
4th dose	11,814	1	0	0	0	0	0	0	
Vaccine types									
AstraZeneca	20,348,852	109,310	331	0.30	17.11	1.63	108	5.58	0.53
Pfizer-BioNTech	72,913,745	232,579	1254	0.54	64.84	1.72	580	29.99	0.80
Morderna	23,778,303	109,153	291	0.27	15.05	1.22	123	6.36	0.52
Janssen	1,508,513	8,836	54	0.61	2.79	3.58	30	1.55	1.99
Novavax	60,259	129	4	3.10	0.21	6.64	0	0	0

- Data were calculated using information on suspected adverse events after COVID-19 vaccination reported by medical facilities or doctors.
- Suspected data were raw data as reported.
- Confirmed data were suggested causality between the vaccines and adverse events by diagnositc eligibility and casuality evaluations.
- No cases of anaphylaxis reported in the pregnant women group during the same period (0 cases)

a) The cases of suspected anaphylaxis reports of each variables / Total AEFI report (proportion,%)
b) The cases of suspected anaphylaxis reports of each variables/ Total suspected anaphylaxis reports (proportion,%)
c) Confirmed cases / Total suspected anaphylaxis reports (proportion,%)

Table 2. The reports of adverse events after receipt of COVID-19 vaccines, by recipients' sex, age group, and type of vaccine : Seoul, from February 26, 2021 to February 26, 2022

Variable	Vaccination dose (case)	Sub-total (case)	Suspected				Confirmed		
			Total (case)	%[a]	%[b]	Adverse events reported per 100,000	Total (case)	%[c]	Confirmed case per 100,000
Total	22,138,149	72,171	534	0.74	100.0	0.44	145	27.15	0.12
Sex									
Male		25,352	151	0.60	28.28		39	7.30	
Female		46,819	383	0.82	71.72		106	19.8	
Age groups									
≤ 19	920,796	3,498	34	0.97	6.37	3.69	12	2.25	1.30
20-29	3,240,982	13,771	143	1.04	26.78	4.41	44	8.24	1.36
30-39	3,403,254	13,069	130	0.99	24.34	3.82	35	6.55	1.03
40-49	3,580,153	11,130	116	1.04	21.72	3.24	31	5.81	0.87
50-59	4,098,090	10,887	61	0.56	11.42	1.49	11	2.06	0.27
60-69	3,745,649	12,632	38	0.30	7.12	1.01	8	1.50	0.21
70-79	2,059,702	5,460	8	0.15	1.50	0.39	1	0.19	0.05
≥ 80	1,044,383	1,724	4	0.23	0.75	0.38	3	0.56	0.29
Vaccine dose									
1st dose	8,301,125	40,253	423	1.05	79.21	5.10	115	21.54	1.39
2nd dose	8,211,655	24,970	90	0.36	16.85	1.10	23	4.31	0.28
3rd dose	5,625,369	6,948	21	0.30	3.93	0.37	7	1.31	0.12
4th dose	0	0	0	0	0	0	0	0	0
Vaccine types									
AstraZeneca		16,564	65	0.39	12.17		13	2.43	
Pfizer-BioNTech		45,694	394	0.86	73.78		109	20.41	
Morderna		8,058	53	0.66	9.93		13	2.43	
Janssen		1,822	20	1.10	3.75		10	1.86	
Novavax		33	2	6.06	0.37		0	0	

- Data were calculated using information on suspected adverse events after COVID-19 vaccination reported by medical facilities or doctors.
- Suspected data were raw data as reported.
- Confirmed data were suggested causality between the vaccines and adverse events by diagnositc eligibility and casuality evaluations.
- Data of total vaccine dose of Seoul were opened partially ; age groups, vaccine dose.
- No cases of anaphylaxis reported in the pregnant women group during the same period (0 cases)

a) The cases of suspected anaphylaxis reports of each variables / Total AEFI report (proportion,%)
b) The cases of suspected anaphylaxis reports of each variables/ Total suspected anaphylaxis reports (proportion,%)
c) Confirmed cases / Total suspected anaphylaxis reports (proportion,%)

3.2 Clinical symptoms of report suspected anaphylaxis and confirmed anaphylaxis after COVID-19 vaccination in Seoul

1. Clinical symptoms of report suspected anaphylaxis

Most of the symptoms were appeared 'Suddenly' and 'Rapidly', some cases were not. 1 of the entire cases (n=534) didn't met the criteria 'Suddenly' and 2 of them didn't met the criteria 'Rapidly' in Seoul.

Most of the patients manifested respiratory (389 cases, 72.9%), cardiovascular (275 cases, 51.5%), cutaneous/mucosal (176 cases, 32.9%), gastrointestinal (135 cases, 25.3%) were also prevalent.

The respiratory symptoms were 389 cases out of 534 cases in total and had the most highest proportion. In details, sensation of throat closure (266 cases), Difficulty breathing without wheezing or stridor (177 cases) were following.

Cardiovascular symptoms, the second most common, were the 275 cases. Hypotension was significantly higher and tachycardia (106 cases), decreased level of consciousness (83 cases) were following.

Cutaneous/Mucosal symptoms were 176 cases. For details, Angioedema (69 cases), Generalized pruritus with skin rash (42 cases), Generalized urticaria were following.

The least number of gastrointestinal symptoms were 135 cases, nausea, vomiting, abdominal pain, diarrhea were prevalent.

The laboratory test result (whether elevated mast cell tryptase) was

absent (0 cases).

In the case of Symptom onset variables, '<15 minutes' were 291 cases were the most highest proportion, '15 ≤ x < 30 minutes' were 132 cases, '60 minutes ≥' 91 cases, 30 ≤ x < 60 minuets' were 20 cases were following. There was a recipients whose symptoms were appeared after 23 days and 10 hours 59 minutes, it was the maximum. In the case of the past history of allergic reactions related drug/food, the answer 'Yes' was 120 cases, 'No' was 414 cases, those who did not experience allergic reactions accounted for a greater proportion of reports.

The treatment at the first symptoms appearance, epinephrine 271 cases(50.7%) were the highest, antihistamine 233 cases(43.6%), glucocortecoids 194 cases(36.3%), applying oxygen 95 cases(17.8%) were following. Items for treatment content can be answered in duplicate, other treatments were recorded directly in the descriptive form, the answer were 'supine position with lifted legs', 'Normal saline hydration', 'P.O medication'. (Table 3)

Table 3. Clinical symptoms of reported suspected anaphylaxis cases after COVID-19 vaccine in Seoul, Korea

Variable	Total	(%)	Vaccine types				
			Pfizer	Moderna	AstraZenca	Janssen	Noavavex
Total	**534**	**100.0**	**394**	**53**	**65**	**20**	**2**
Suddenly							
Yes	533	99.81	394	53	64	20	2
No	1	0.19	0	0	1	0	0
Rapidly							
Yes	532	99.63	394	53	64	19	2
No	2	0.37	0	0	1	1	0
Cutaneous or mucosal							
Observed	176	32.96	131	16	22	6	1
Not Observed	358	67.04	263	37	43	14	1
Generalized pruritus without skin rash	29	5.34	23	4	0	2	0
Generalized prickle sensation	25	4.68	21	0	4	0	0
Localized injection site urticaria	24	4.49	16	3	4	1	0
Red and itchy eyes	26	4.87	18	2	6	0	0
Generalized urticaria	39	7.30	28	4	6	0	2
Generalized erythema	13	2.43	10	2	1	0	0
Angiodema	69	12.92	50	6	10	3	0
Generalized pruritus with skin rash	42	7.87	30	5	6	0	1
Cardiovascular							
Observed	275	51.50	205	25	34	11	0
Not Observed	259	48.50	189	28	31	9	2
≥ 2 signs of reduced peripheral circulation							
Tachycardia	69	12.92	51	3	14	1	0
Capillary refill > 3 seconds	7	1.31	5	1	1	0	0
Decreased level of consciousness	47	8.80	34	6	6	1	0
Measured hypotension	133	24.91	104	12	9	8	0
≥ 3 signs of uncompensated shock:							
Tachycardia	37	6.93	26	4	6	1	0
Capillary refill > 3 seconds	11	2.06	7	2	1	1	0
Reduced central pulse volume	9	1.69	7	1	0	1	0
Decreased level or loss of consciousness	36	6.74	27	5	2	2	0
Respiratory							
Observed	389	72.85	286	36	51	14	2
Not Observed	145	27.15	108	17	14	6	0
Persistent dry cough	35	6.55	25	3	7	0	0
Hoarse voice	28	5.24	24	2	2	0	0
Difficultly being without wheeze or stridor	177	33.15	135	12	28	2	0
Sensation of throat closure	226	42.32	176	22	20	6	2
Sneezing or rhinorrhea	7	1.31	6	1	0	0	0
Bilateral wheeze (bronchospasm)	16	3.00	12	2	0	1	1
Stridor	10	1.87	6	2	1	1	0
Upper airway swelling	67	12.55	45	7	11	3	1
≥ 2 indicators of respiratory distress : Tachycardia, Cyanosis, Grunting, Chest wall retractions Increased use of accessory respiratory muscles	28	5.24	21	3	2	1	1
Gastrointestinal							
Observed	135	25.28	97	13	16	7	2

	Not Observed	399	74.72	297	40	49	13	0
	Diarrhea	4	0.75	3	0	1	0	0
	Abdominal pain	22	4.12	18	2	1	1	0
	Nausea	121	22.66	89	9	14	7	2
	Vomiting	33	6.18	20	6	5	2	0
Laboratory test								
	Did	0	0.0	0	0	0	0	0
	Elevated mast cell tryptase	0	0.0	0	0	0	0	0
	Didn't	534	100.0	394	53	65	20	2
Onset								
	> 15 min	291	54.49	219	30	28	13	1
	15≤ X <30 min	132	24.72	97	13	16	5	1
	30≤ X <60 min	20	3.75	16	1	2	1	0
	≤ 60min (max : 23days 10hours 59minutes)	91	17.04	62	9	19	1	0
Past history								
	Yes	120	22.47	86	7	19	7	1
	No	414	77.53	308	46	46	13	1
Treatment								
	Epinephrine	271	50.75	198	25	32	16	0
	Antihistamine	233	43.63	167	23	34	8	1
	Glucocortecoids	194	36.33	144	16	30	3	1
	Oxygen	95	17.79	64	5	22	4	0

2. Clinical symptoms of confirmed anaphylaxis

After the report as anaphylaxis after COVID-19 vaccination, a total of 145 cases, which were satisfied both diagnostic eligibility and BCCD criteria for causality, were analyzed by recipient's medical records for the study.

Clinical symptoms in the confirmed cases of Seoul were observed 'suddenly' and 'rapidly' at the most of cases. Except of 1 case didn't satisfy the 'rapidly' but confirmed as a delayed anaphylaxis symptom. The demographic characteristic of the recipient were women, 40-49 years, 1st dost of Jassen, lived in seoul. The first symptom was appeared in 30 minutes after vaccination, the treatment for early phase were epinephrine, antihistamine, glucocortecoids, applying oxygen. According to medical records, the diagnosis was

‘Anaphylaxis’, the chief complaints were Cutaneous(swelling, redness) and respiratory symptom (Vocal change). After treatment, the same symptoms were consistent for few days. 2 times visit outpatient department for treatment. According to those history, this case was evaluated as a level 1 in final.

Symptoms were the same trend as the report part. Most of the patients manifested respiratory (110 cases, 75.9%), cardiovascular (85 cases, 58.6%), Cutaneous/mucosal (66 cases, 45.5%), gastrointestinal (51 cases, 35.2%) were also prevalent.

The most common symptoms in the respiratory were also consistent with the analysis of reported cases. In details, sensation of throat closure (57 cases), Difficulty breathing without wheezing or stridor (44 cases) were following.

The second most common symptoms in the cardiovascular were also consistent with the analysis of reported cases. Hypotension (65 cases) was the highest, tachycardia (25 cases), decreased level or loss of conscious (22 cases) were following. On Cutaneous/mucosal symptoms, there was a difference from the analysis of reported cases.

Generalized or localized angioedmea was 28 cases and the highest. However, Generalized pruritus with skin rash was the most second common symptom as 19 cases.

The gastrointestinal symptoms were appeared in order to nausea (48 cases), abdominal pain (10 cases), vomiting (9 cases), unlikely the analysis of reported cases, diarrhea was none.

The laboratory result was absent as following the result of the reported cases.

The result of symptom onset was the same trends to the analysis of the reported cases. '<15 minutes' were 83 cases were the most highest proportion, '15 ≤ x < 30 minutes' were 33 cases, '60

minutes ≥′ 24 cases, 30 ≤ x < 60 minuets′ were 5 cases were following.

In the case of the past history of allergic reactions related drug/food, the answer 'Yes' was 32 cases, 'No' was 113 cases, those who did not experience allergic reactions accounted for a greater proportion of reports. It showed a similar flow to the report analysis data.

The treatment at the first symptoms appearance, epinephrine 93 cases(64.1%) were the highest, antihistamine 72 cases(49.6%), glucocortecoids 60 cases(41.4%), applying oxygen 29 cases(20.0%) were following. Items for treatment content can be answered in duplicate. (Table 4)

Table 4. Clinical symptoms of confirmed anaphylaxis cases after COVID-19 vaccine in Seoul, Korea

Variable	Total	(%)	Vaccine types				
			Pfizer	Moderna	AstraZenca	Janssen	Noavavex
Total	**145**	**100.0**	**109**	**13**	**13**	**10**	**0**
Suddenly							
Yes	145	100.0	109	13	13	10	0
No	0		0	0	0	0	0
Rapidly							
Yes	144	99.31	109	13	13	9	0
No	1	0.69	0	0	0	1	0
Cutaneous or mucosal							
Observed	66	45.52	51	5	7	3	0
Not Observed	79	54.48	58	8	6	7	0
Generalized pruritus without skin rash	6	4.14	4	1	0	1	0
Generalized prickle sensation	8	5.52	8	0	0	0	0
Localized injection site urticaria	4	2.76	2	0	2	0	0
Red and itchy eyes	8	5.52	5	1	2	0	0
Generalized urticaria	19	13.10	17	0	2	0	0
Generalized erythema	6	4.14	6	0	0	0	0
Angiodema	28	19.31	20	1	5	2	0
Generalized pruritus with skin rash	19	13.10	14	2	3	0	0
Cardiovascular							
Observed	85	58.62	66	7	7	5	0
Not Observed	60	41.38	43	6	6	5	0

	≥ 2 signs of reduced peripheral circulation							
	Tachycardia	13	8.97	11	1	1	0	0
	Capillary refill > 3 seconds	1	0.69	1	0	0	0	0
	Decreased level of consciousness	10	6.90	8	1	0	1	0
	Measured hypotension	65	44.83	48	7	5	5	0
	≥ 3 signs of uncompensated shock:							
	Tachycardia	12	8.28	7	1	4	0	0
	Capillary refill > 3 seconds	7	4.83	5	1	1	0	0
	Reduced central pulse volume	4	2.76	3	0	0	1	0
	Decreased level or loss of consciousness	12	8.28	7	2	1	2	0
Respiratory								
	Observed	110	75.86	83	10	11	6	0
	Not Observed	35	24.14	26	3	2	4	0
	Persistent dry cough	12	8.28	9	1	2	0	0
	Hoarse voice	8	5.52	7	1	0	0	0
	Difficultly being without wheeze or stridor	44	30.34	39	2	3	0	0
	Sensation of throat closure	57	39.31	46	5	3	3	0
	Sneezing or rhinorrhea	1	0.69	1	0	0	0	0
	Bilateral wheeze (bronchospasm)	7	4.83	5	1	0	1	0
	Stridor	6	4.14	4	1	1	0	0
	Upper airway swelling	22	15.17	13	2	5	2	0
	≥ 2 indicators of respiratory distress : Tachycardia, Cyanosis, Grunting, Chest wall retractions Increased use of accessory respiratory muscles	32	22.07	23	2	4	3	0
Gastrointestinal								
	Observed	51	35.17	38	2	5	6	0
	Not Observed	94	64.83	71	11	8	4	0
	Diarrhea	0	0.0	0	0	0	0	0
	Abdominal pain	10	6.90	9	0	0	1	0
	Nausea	48	33.10	35	2	5	6	0
	Vomiting	9	6.21	6		1	2	0
Laboratory test								
	Did	0	0.0	0	0	0	0	0
	Elevated mast cell tryptase	0	0.0	0	0	0	0	0
	Didn't	145	100.0	109	13	13	10	0
Onset								
	> 15 min	83	57.24	62	5	8	8	0
	15≤ X <30 min	33	22.76	23	7	2	1	0
	30≤ X <60 min	5	3.45	5	0	0	0	0
	≤ 60min (max : 23days 10hours 59minutes)	24	16.55	19	1	3	1	0
Past history								
	Yes	32	22.07	21	1	6	4	0
	No	113	77.93	88	12	7	6	0
Treatment								
	Epinephrine	93	64.14	69	7	8	9	0
	Antihistamines	72	49.66	49	8	10	5	0
	Glucocortecoids	60	41.38	46	4	8	2	0
	Oxygen	29	20.00	18	2	5	4	0

3.3 Risk factors and the correlation

1. Selection of Risk factors

The variables were selected from the demographic information which were required to report as AEFI / AESI on the KDCA's vaccine management system after COVID-19 vaccination.

There were sex, age groups, vaccine type (excluded the past), vaccine dose. Compared to result of descriptive statistic analysis based on the reported cases between Korea and Seoul, women, 20-29 years, after 1st dose, the Pfizer-BioNTech COVID-19 vaccine were in common and had the highest proportion.

Additionally, the risk factor selected is whether the recipient has experienced previous allergic reactions related to drug/food. The past history of allergic reactions related to drug/food were gathered from the basic survey of anaphylaxis after COVID-19 vaccination by interviewing with recipients. The reason for including the past history of allergic reaction related to drug/food was based on the anaphylaxis manual after COVID-19 vaccination by the KDCA. According to the anaphylaxis manual after the COVID-19 vaccination, Allergies to certain drugs such as allergic rhinitis, atopic dermatitis, food allergies, urticaria, insect poison allergies, animal allergies, allergic family history, local reactions after previous vaccinations, and hypersensitivity reactions after vaccination of other ingredients were classified into high/medium/low risk groups. And there was a difference in the follow-up time after COVID-19 vaccination.

Another reason for including the past history of allergic reaction related to drug/food was the results of descriptive statistics on reported data and data confirmed for anaphylaxis causality with COVID-19 vaccination. According to the Seoul Metropolitan Government's report, 120 people answered that they had previously experienced allergic reactions related to drug/food, and 414 people answered that they had not. At confirmed cases, there were 32 and 113, respectively. Contrary to the recommendations in the manual presented by the KDCA, the COVID-19 recipients who had no past history of allergic reactions related drug/food accounted for a greater percentage of anaphylaxis after COVID-19 vaccination. Therefore, tried to check the correlation, including the presence or absence of the past history of allergic reactions related to drug/food. However, since the previous experience of allergic reactions was collected through interviews, the data is subjected by the recall bias. Since it was not a cohort study, it was not possible to confirm the history of the COVID-19 recipients' past history of diseases in detail. Instead, the medical institution in Seoul tried to reduce the possibility of recall bias by reviewing all 534 related medical records reported as suspected cases of anaphylaxis after the COVID-19 vaccination. Among the confirmed case of anaphylaxis after COVID-19 vaccination, in an interview with the report as suspected anaphylaxis after COVID-19 vaccination, 32 people answered that they had previous allergic reaction experience, and 113 people answered that they had not experienced the previous allergic reaction. However, when reviewing their medical records, it was finally confirmed that 62 people had previous allergic reaction experiences and 83 people (including one unresponsive person) had no allergic reaction

experience. Data that have completed the review of medical records were used as risk factor data for correlation analysis.

After descriptive statistic analysis, the vaccine dose was excluded from the risk factors in this study. Because COVID-19 vaccination policy in Korea was affected in correlation as a confounding variable.

In this study, when the recipient was reported as anaphylaxis after the 1st COVID-19 vaccine dose, it was excluded from the 2nd vaccine subjects. In this way, The same applies to 3rd and 4th vaccine dose, and there was no duplicates in this study. If so, it was natural that among the data reported as anaphylaxis, there were the most cases after the first dose. They can be called the high risk group and impossible to vaccinate. From the second dose, it can be assumed that the number of anaphylaxis reports will gradually decreased and could be directly confirmed as a result of the descriptive statistics of the reported data. The problem is that unlike other VPD (Vaccine Preventable Disease), COVID-19 vaccine is not a monotype. In shorts, 'mix-and-match vaccination' could be a confounding variable in this study. If someone who experience a adverse events following COVID-19 vaccination, it is impossible to vaccinate the same platform (viral vector, mRNA etc.) as before.[30] For examples, when a recipient was vaccinated AstraZenca on 1st dose, and then reported as anaphylaxis. Although The recipient was vaccinated Pfizer Bio-NTech on 2nd dose, the recipient experience anaphylaxis symptoms again. If then, there will be duplicates on the report data. Fortunately, there was no duplicates on the report data of Seoul, but the national range data couldn't check the duplicate because these were base on public materials from KDCA.

In other words, to examine correlation between vaccine dose and

anaphylaxis following COVID-19 vaccine, it is required to control various variables such as vaccine type, whether mix-and-match vaccination or not, appearance of symptoms after the mix-and-match vaccination.

In addition, the timing of mix-and-match vaccination also could be a confounding variable. The early phase of COVID-19 vaccination campaign in Korea, the high-risk group for infection (≥70 years old age group) to COVID-19 vaccinated AstraZenca COVID-19 vaccine in the first order. At that time, Pfizer Bio-NTech COVID-19 vaccine was rarely vaccinated. As the number of reports and suspected cases of severe adverse events, including thrombocytopenia and capillary leakage syndrome, in AstraZeneca vaccination groups worldwide increases, the vaccination was temporarily suspended in early April 2021. And then KACIP recommended the recipient who was scheduled to be vaccinated AstraZenca, changed their vaccine types to other platform and the mix-and-match vaccination was allowed since then. Additionally, the timing of vaccination was depended on age groups.

Therefore, to examine correlation between vaccine dose and anaphylaxis following COVID-19 vaccine, it is required to consider other ways to manage confounding variables. Due to the risk of confounding that may occur for each variable, the thesis of this study may be blurred, so it was excluded. (Table 5)

Table 5. The reported cases of anaphylaxis after COVID-19 vaccination in Korea by recipients' type of vaccine, vaccine dose

Variable		Vaccination dose	Suspected	Confirmed	%[a)]	%[b)]
Vaccine types	Dose					
Total		118,609,672	1,934	841	-	-
Astra Zeneca	Total	20,348,852	331	108	17.11	12.84
	1st	11,097,354	289	95	87.31	87.96
	2nd	9,251,372	41	13	12.39	12.04
	3rd	126	1	0	0.03	0.00
Pfizer-BioNTech	Total	72,913,745	1,254	580	64.84	68.96
	1st	25,254,362	951	459	75.84	79.14
	2nd	26,810,539	236	101	18.82	17.41
	3rd	20,837,717	67	20	5.34	3.45
	4rd	11,127	0	0	0.00	0.00
Moderna	Total	23,778,303	291	123	15.05	14.62
	1st	6,764,985	219	97	75.26	78.86
	2nd	6,586,683	45	13	15.15	10.57
	3rd	10,425,948	27	13	9.59	10.57
	4rd	687	0	0	0.00	0.00
Janssen	Total	1,508,513	54	30	2.79	3.56
	1st	1,482,530	53	29	98.15	96.67
	2nd	25,983	1	1	1.85	3.33
Novaves	Total	60,259	4	0	0.21	0.00
	1st	43,443	4	0	100.0	0.00
	2nd	2,876	0	0	0.00	0.00
	3rd	13,940	0	0	0.00	0.00

- Data were calculated using information on suspected adverse events after COVID-19 vaccination reported by medical facilities or doctors.
- Suspected data were raw data as reported.
- Confirmed data were suggested causality between the vaccines and adverse events by diagnositc eligibility and casuality evaluations.

a) The cases of suspected anaphylaxis reports of each variables / The total reports of suspected anaphylaxis of each vaccine types

b) The cases of confirmed anaphylaxis of each variables / The total confirmed cases of each vaccine types

2. Result of Analysis

In this study, the condition of the analysis target is 'a person who has been COVID-19 vaccine vaccinated'. There was no difference in whether or not to be vaccinated against COVID-19, and among those

who were vaccinated against COVID-19, those who reported suspected anaphylaxis were targeted.

Stratified data of the reported suspected anaphylaxis by the evaluation of diagnostic eligibility into 2 groups, 'Anaphylaxis', 'Not anaphylaxis' to examine correlation between variables which were selected prior and incidence of anaphylaxis after COVID-19 vaccination. The group of 'Anaphylaxis' was a total of 145 cases. They were assessed the level 1, 2, 3 of diagnostic eligibility based on BCCD. The group of 'Not Anaphylaxis' was a total of 389 cases. There were assessed the level 4 of diagnostic eligibility based on BCCD. Those who were assessed the level 5 of diagnostic eligibility were not anaphylaxis case, also they had the possibility of another disease. So they excluded in this study.

By borrowing the concept of case-control study, these two groups were compared by using those identified as anaphylaxis as a case group and those who were confirmed 'not anaphylaxis' as a control group, and how much risk factors selected by each group accounted for. The two groups are summarized by risk factors as follows.

In 'Anaphylaxis', 39 were men (26.9%), 106 were women(73.1%), the median age was 34±15.55 years. (13-92 years) Pfizer had 109 cases (75.2%), Moderna and AstraZeneca had 13 cases (8.9%), Jansen had 10 cases (6.9%), and Novavax had 0 cases. Previously, 62 (42.8%) had experienced allergies to drugs or foods, 82 (56.5%) had none, and 1 (0.7%) had no knowledge. 'no knowledge' was considered 'no'. The mean symptom onset was 82.82±18.47 minutes. (min 1minutes, max 1467 minutes)

In 'Not anaphylaxis' 96 were men(28.2%), 244 were women (71.8%), the median age was 36±13.56 years. (12-81 years). Pfizer

had 261 cases (76.8%), AstraZeneca had 34 cases (10.0%), Moderna had 33 cases (9.7%), Jansen had 10 cases (2.9%), and Novavax had 2 cases (0.6%). Previously, 72 (21.2%) had experienced allergies to drugs or foods, 15 (4.4%) had none, and 253 (74.4%) had no knowledge. The mean symptom onset was 47.07±8.21 minutes. (min 0minutes, max 1260 minutes) The proportion of each risk factors in Anaphylaxis group among the total report case in Seoul was as follow. In sex, 7.3% were men, 19.8% were women. And the vaccine type was followed by Pfizer 20.41%, Astrazeneka and Morderna 2.43%, Janssen 1.86%. The proportion who had the past history of allergic reaction was 11.61%, who did not have the allergic reaction before was 15.36%. (Table 6)

Each variable was compared the result of Proportional Mortality Rate related Odds ratio(below PMR r/t Odds ratio) using the chi-square test. PMR r/t Odds ratio of The past history of allergic reaction related drug/food was 2.78, and the Jassens COVID-19 vaccine was 2.44. (Table 7)

Along with age, sex, vaccine type, the past history of allergic reaction were included in the multiple regression analysis. The onset time was excluded in the multiple regression analysis because only for the symptom onset within 24 hours was confirmed as anaphylaxis according to COVID-19 vaccination policy in Korea. Sex and age group were insignificant and the null hypothesis was adopted in conclusion. The vaccine type was p-value=0.88 and the null hypothesis was adopted. However, the PMR r/t Odds ratio of the vaccine type was higher on table 7, this point is need to re-discuss.

Then in Anaphylaxis group, variables were analyzed by the multiple regression. The result is that only 'the past history of allergic

reaction related drug/food' was p-value < 0.05. (Table 8)

In this study, Odds ratio is the Proportional Mortality Rate related Odds ratio. Because the characteristics of the data which was reported. In other words, this is not cohort study or case-control study. It is data on those who have anaphylaxis among those who have been vaccinated for a certain period of time so it can be seen as the concept of the Professional Mortality Rate.

In the case of Jassens COVID-19 vaccines, the PMR r/t Odds ratio was higher and it was significant. But in the multiple regression analysis, the vaccine types were stratified by platform into 2 groups, 'Viral vector platform' and 'mRNA platform'. Jassens COVID-19 vaccines were included in Viral vector platform. After that, in the multiple regression analysis, the result of the vaccine types adopted the null hypothesis. (p-value > 0.05)

However, In terms of vaccine manufacturers, It can be thought anew in that the PMRr/t Odds ratio of the Janssen vaccine produced significant results.

Table 6. The comparison of characteristic between group 'Anaphylaxis' and group 'Not anaphylaxis' in confirmed anaphylaxis cases after COVID-19 vaccination in Seoul

Variables		Total report (proportion[a]) (n=534)	Anaphylaxis (proportion[a]) (n=145)	Not anaphylaxis (proportion[a]) (n=340)
Sex(n)	Male	151	39 (26.9)	96 (28.2)
	Female	383	106 (73.1)	244 (71.8)
Age(median±SD)(yr)		36±14.61	34±15.55	36±13.56
Vaccine types	Pfizer	394	109 (75.2)	261 (76.8)
	Moderna	53	13 (8.9)	33 (9.7)
	AZ	65	13 (8.9)	34 (10.0)
	J&J	20	10 (7.0)	10 (2.9)
	Novavax	2	0	2 (0.6)
The past history of allergic reaction (food/drug)	Y	120	62 (42.8)	72 (21.2)
	N	414	82 (56.6)	15 (4.4)
	None	-	1 (0.6)	253 (74.4)
Time(mean±SE)(min)		57.76±7.99	82.82±18.47	47.07±8.21

a) Each variables / Each group total

- Data are presented as median (especially age, time) or n (%)
- Exclusion : 11 cases of the BCCD result 'None'

Table 7. Results of Chi-square test analysis in confirmed anaphylaxis cases after COVID-19 vaccination in Seoul (n=145)

Variables	Odds ratio	95% CI	p-value
Incidence by gender			
Male	1		
Female	0.94	0.604-1.447	0.763
Incidence by age groups (years)			
10-19	1		
20-49	1.13	0.721-1.775	0.591
50≤	0.75	0.449-1.267	0.285
Incidence by vaccine types			
Pfizer	1		
Moderna	0.92	0.467-1.797	0.799
AZ	0.89	0.453-1.734	0.724
J&J	2.44	0.994-6.007	0.045
Novavax	0	0.0	0
Incidence by the past history of allergic reaction related to drug/food			
No	1		
Yes	2.78	1.828-4.229	0.000001

Table 8. Result of multiple regression analysis in confirmed anaphylaxis cases after COVID-19 vaccination in Seoul (n=145)

Character	95% Wald confidence interval		p-value
Sex(n) (M:F)	-0.07	0.08	0.86
Mean age(yr)	-0.07	0.08	0.91
Vaccine platform	-0.10	0.09	0.88
The past history of allergic reaction (food/drug)	0.11	0.27	0.000003

3.4 A review on the anaphylaxis diagnostic eligibility criteria, BCCD

Group ② determined by the prior test for selection study group was a total of 534. The expected value was the level of determined automatically on the KDCA's management system. The test result was the conclusion level of assessed by BCCD.

The results is that True-Positive:102, False-Negative:290, True-Negative:43, False-Positive:88 (values represent case) and Sensitivity:26%, specificity:33%. 'Figure 2' is the ROC curve of the result. Calculated AUC was 0.73, according to criteria of Muller(2005)[67], it means 'Fair' within the $0.7 \leq AUC < 0.8$.

Table 9. The comparison of report with BCCD results (n=534)

Frequency chart		BCCD		Total
		True	False	
Report	Positive	102	88	190
	Negative	43	290	333
Total		145	378	523

- Report means that the automatically determined results by field staffs according to BCCD on KDCA management system (Level 1,2,3 is positive, Level 4,5 is negative)
- BCCD means that the confirmed results by experts through the evaluation steps for diagnostic eligibility and casuality. (Level 1,2,3 is positive, Level 4,5 is negative)
*see 2.3.3. the validity of diagnostic eligibility evaluation criterial of anaphylaxis
- exclusion : 11 cases of the BCCD result 'None'

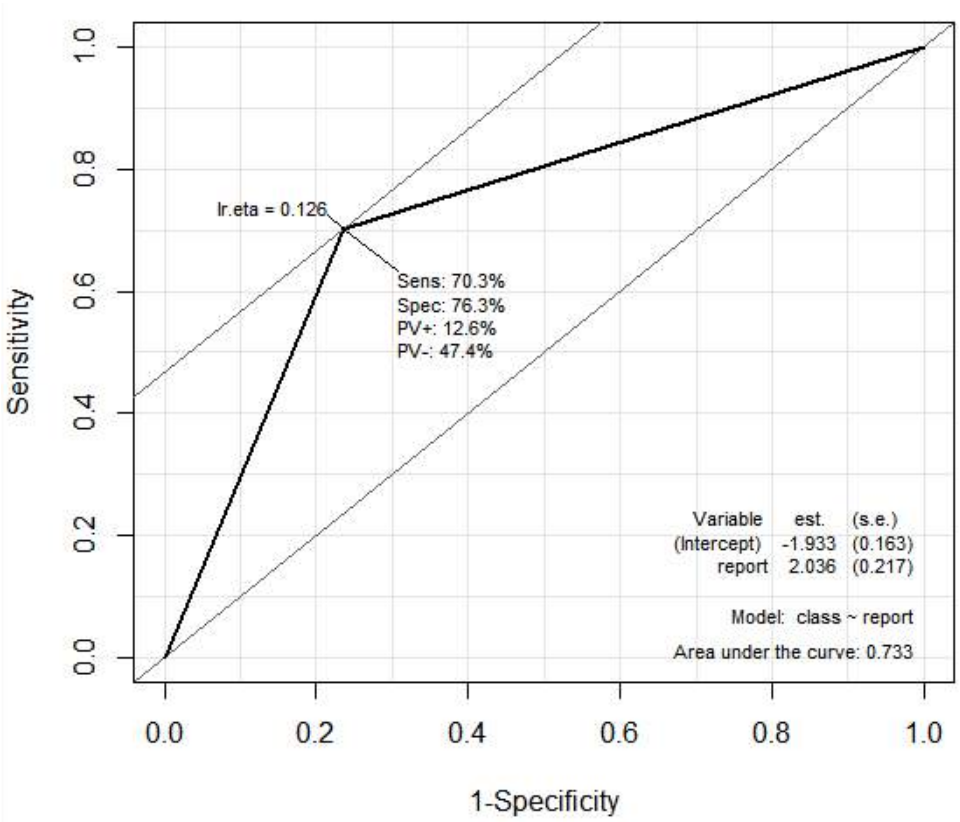

Figure 3. ROC curve of the result that comparison with report and BCCD (table 2)

Chapter 4. Conclusion

4.1 Limitation

The findings in this study are subject to at least four limitations.

First, this study is a retrospective study based on data reported as an adverse events after being vaccinated against COVID-19, like previous studies on the current status and cause analysis of anaphylaxis in Korea.

Secondly, the suspected anaphylaxis case reports were gathered through active surveillance based on spontaneous reports to VAERS. Spontaneous reporting is subject to reporting biases (including under reporting). As mentioned above in Chapter 2-Material and Methods-another limitation is the inaccuracy of reported data due to the reporting bias. Demographic information is relatively accurate because it is based on the resident registration system. On the other hand, the information on the basic survey of anaphylaxis is rarely unstable. Because it depends on who reported it. For example, several cases' reporter were medical institutions that did not experience the anaphylaxis situation in person. And there were various cases which were submitted with blanks.

In addition, the data on reporting adverse events after COVID-19 vaccination, which was the basis of this study, was greatly affected by the vaccination policy of the Republic of Korea, and it also had a significant impact on reporting adverse events. A representative example is the introduction of a quarantine policy called 'vaccine

pass' (since 2021.11.01. in Korea). As a result of the vaccine pass implementation, increased the report of false-positive anaphylaxis symptoms or reported late gradually. (There was a difference of up to 90 days between vaccination and onset of symptoms.) however, the reporting efficiency to VAERS for clinically severe adverse events is believed to be high.

Third, One of the key risk factors in this study is the past history of allergic reaction gathered by interview. It is possible that the interview was dependent on the recipients' memories only. For this reason, the information of one's allergic history before the COVID-19 vaccination is subject to the recall biases.

In the same way, there is insufficient information about the past history of allergic reaction. The basic survey of anaphylaxis is only asking about past allergic reaction experiences with drugs or foods. In previous anaphylaxis studies, as a trigger, the correlation was reviewed by confirming atopy, asthma, allergic rhinitis, chronic urticaria, cardiovascular disease, long-term use of antihistamine or other drugs. However, in this study, detailed categories could not be identified due to lack of related data.

The last one is the absence of standardization tools for anaphylaxis after vaccination. On the other words, Anaphylaxis after vaccination is diagnosed on a different criteria at every hospital and vaccination center. It was found by comparing the suspected anaphylaxis report and causality assessment data with the medical record review. The problem is that there was a difference between medical record and diagnostic eligibility result. However, In this study, all the medical records of the report as anaphylaxis after COVID-19 vaccination were reviewed to prevent misleading results due to those differences. Also the casuality results assessed with the diagnostic eligibility by BCCD

was a one way to solve this limitation. Nevertheless, it is necessary to confirm whether BCCD is applied as an anaphylaxis diagnostic tool in the medical field through other studies.

4.2 Discussion

This study began with the question of why the suspected report rate of anaphylaxis after COVID-19 vaccination in Korea is higher than that of other countries.

Q1. Before the COVID-19 vaccination campaign, what was the incidence rate of anaphylaxis related to vaccines in Korea?

The incidence of anaphylaxis in Korea increased recently. The incidence of anaphylaxis below the 18 years old per 100,000 population was 0.70-1.0 in 2001-2007[68], 3.0-11.6 in 2007-2013.[37] Nevertheless, the incidence of vaccine-related anaphylaxis has been reported very little, the incidence rates of vaccine-related anaphylaxis per million dose was 0.090 in 2005, 0.079 in 2012, 0.071 in 2013, 0.188 in 2015, 0.036 in 2016.[49] During the pandemic of H1N1 in 2009, the mass vaccination campaign was implemented, the main cause of exploding of reporting adverse events after vaccination was Influenza vaccine before the appearance of COVID-19. As analyzed in this study, for every 100,000 doses, 1.63 cases were reported and 0.71 cases were confirmed the causality in Korea during COVID-19 vaccination campaign. Except the mass vaccination campaign against the influenza virus in 2009, there were less than one vaccine-related anaphylaxis case a year. After the COVID-19 vaccination start, the

incidence rate of vaccine-related anaphylaxis cases were increased both abroad and at home.

Q2. What characteristics do the cases reported as suspected anaphylaxis after COVID-19 vaccination in Korea have?

In the analysis of the report as a suspected anaphylaxis after COVID-19 vaccination data, no difference was found between the entire data of Korea and the Seoul's. Women were more higher than men. Those who were aged 20-29 years had the highest rate among all age groups (12 years~≤ 80 years) getting older, the proportion of reporting anaphylaxis decreased. Pfizer-BioNTech vaccine in vaccine type, 1st vaccine dose recipients take the most proportion of it. As the number of vaccination dose increased, the number of reports of anaphylaxis decreased. Of reports with time to onset of symptoms <15 minutes were the highest proportion and 30≤ x < 60 minutes were the lowest. The longest onset of symptom was 1days and 27 minutes after vaccination. Contrary to previous research, most of recipient who didn't experience of allergic reaction to drug or food before reported as suspected anaphylaxis after COVID-19 vaccination.

Trough the above descriptive analysis, the characteristics that occupy a large proportion in the reported cases were found. These characteristics were selected as risk factors, believing that they were related to the incidence of anaphylaxis in the COVID-19 vaccination group. Selected risk factors were the Age, Sex, Vaccine types, the past history of allergy reactions for drugs or foods of COVID-19 vaccine recipients. Among them, it was necessary to discuss the vaccination dose and the past history of allergic reaction reactions related to drug/food.

- vaccination dose : this was affected by the vaccine policy of Korean government such as vaccination timing, mix-and-match etc. Due to the risk of confounding, this was excluded.

- the past history of allergic reaction related to drug/food : To reduce the possibility of recall bias by reviewing medical records reported as suspected cases of anaphylaxis after being vaccinated with COVID-19.

The correlation between the selected risk factors and anaphylaxis after COVID-19 vaccination was analyzed. The subject of correlation analysis were the COVID-19 vaccine recipients and those who were reported as anaphylaxis in Korea. The subjects were stratified with two groups, 'Anaphylaxis' and 'Not anaphylaxis' by evaluating steps. With the 'Anaphylaxis' group, the PMR related Odds ratio and p-values were calculated for each selected risk factors. There was a difference between the types of vaccines, especially the past history of allergic reaction related drug/food had the correlation to incidence of anaphylaxis after COVID-19 vaccination. The PMR related Odds ratio was 2.78 the highest score and the p-value was very lower than other risk factors by calculating in multiple regression analysis.

Q3. It is noteworthy that the difference between the results of previous studies and the major clinical symptoms in this study. Wouldn't it be a tool to evaluate diagnostic eligibility to affect the increase in the suspected anaphylaxis report rate after COVID-19 vaccination? Are tools for evaluating diagnostic eligibility well used in Korea?

According to epidemiological studies on anaphylaxis caused by drugs, one of the main causes of anaphylaxis in Korea, the most frequent

clinical symptoms of anaphylaxis were Cutaneous/mucosal symptoms like itching sensation, urticaria, redness, swelling of lips/tongue/oral etc took 80-90% of the entire anaphylaxis patients.[23] And the proportion of Respiratory symptoms (rhinorrhea, sneezing, cough, dyspnea, chest discomfort, wheezing) were 70%, Gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhea) were 30-45%, Cardiovascular symptoms (chest pain, hypotension, shock etc) were 10-48%, Neurological symptoms (loss of conscious, faint) were 10-15%.

Clinical symptoms appeared in the order of cardiovascular symptoms, cutaneous/mucosal symptoms, respiratory symptoms, and gastrointestinal symptoms. It was different from the proportion of report of suspected anaphylaxis after COVID-19 vaccination mainly respiratory(66.7%) and cardiovascular(53.7%) took the part.

In the case of drug induced anaphylaxis, clinical symptoms appeared in order to urticaria, hypotension, dizziness, faint, angioedema. On the contrary, in the report of suspected anaphylaxis after COVID-19 vaccine, clinical symptoms were appeared in order to sensation of throat closure, hypotension, difficulty breathing without wheezing or stridor, nausea. And the COVID-19 vaccine recipient who didn't appear cutaneous/mucosal symptoms were 991cases(71.2%). This was the most different from the previous studies in Korea.

In a relatively recent study, the symptoms in patients with anaphylaxis were: Cutaneous symptom (>90%), respiratory (83.25), gastrointestinal (48.9%), neurological (30.3%) and cardiovascular (28.1%) symptoms. On the other hand, studies on vaccine-related anaphylaxis have shown that cardiovascular symptoms (84.6%),

respiratory (61.5%), cutaneous (46.2%) and gastrointestinal system (38.5%) symptoms[49]were following. Compared to the two previous studies, clinical symptoms after COVID-19 vaccination were shown differently.

Also there was another difference that was the COVID-19 vaccine recipients' chief complaints between the reports as a anaphylaxis after vaccination and their medical records. The reports said the respiratory symptoms were the most frequent occurrence but their medical records did not. For example, 'sensation of throat closure' or 'difficulty breathing without wheezing or stridor' were checked at the basic survey of the report, but in the medical records, the recipients said 'feel a pressure on chest' or 'difficult to breath'. Those were more close to the 'chest discomfort' of cardiovascular symptoms.

And in the case of cardiovascular symptoms that is the second most in this study, hypotension and tachycardia were the most frequent answer on the basic survey of anaphylaxis. Although the result of vital signs measured on the symptom onset met the criteria, the past disease history of the COVID-19 vaccine recipients was absent on the medical records. It was impossible to check the relation whether the symptoms were caused by COVID-19 vaccination or not. In the Roh's study[49] (2020) median time of symptom onset was 11minutes without the past history of anaphylaxis or allergy reaction. Compared to this result, In this study, Onset was delayed including recipients who had the past history of allergic reactions.

The validity of BCCD was measured by the report data for suspected anaphylaxis and the evaluation result of diagnostic eligibility were placed as predicted values and diagnostic results, respectively. The result was that sensitivity 26%, specificity 33% and

AUC was 0.73 by ROC curve. The validity of BCCD in Korea is 'Fair' according to Muller's criteria. ($0.7 \leq AUC < 0.8$)

Q4. Then, why is the rate of reporting anaphylaxis high after COVID-19 vaccination unlike other vaccines in Korea?

First, The absence of a standard criteria to be applied to diagnose anaphylaxis for the vaccination center, the medical center and the AEFI department of government could be the answer to this problem. BCCD is applied only to AEFI evaluation. when rechecked the medical records of the report in this study, there were no records that the diagnosis was made by applying BCCD at the medical center. And also on the records of the vaccination center (could be a local medical center), there was absent information of it.

As the incidence of anaphylaxis increases, several countries have reported on the understanding of the disease to medical staff and cooperative medical staff. Even in the previous study, there was still a lack of understanding of the symptoms, diagnosis, and treatment of anaphylaxis[68], and emphasizes the need for systematic education.[69)70)] Knowledge of specific treatment guidelines of anaphylaxis and actual training should be regularly provided to medical staff and cooperative medical staff.

Secondly, In order to increase the understanding of the anaphylaxis main symptoms and recognizing differences with anaphylaxis and other diseases, it is necessary to reorganize the guidelines that the medical staffs respond immediately anaphylaxis situations at the vaccination centers or medical centers.

The algorithm announced by BCCD is translated into Korean and used to evaluate eligibility of anaphylaxis after COVID-19 vaccination.

Since the overall contents are contained in one schematic diagram, detailed explanations of symptoms and additional explanations for each situation are lacking. Therefore, detailed explanations about the symptoms of anaphylaxis by system are not accurately delivered to the medical staffs in vaccination center. For example, It is very difficult to discriminate directly the difference between 'local or generalized angioedema' and 'swelling of upper airway' by only the symptoms of the patient without further explanations. Because the patient's complaint is subjective and there is so many ways to express the same symptom by people. These make difficult to determine the exact site and the severity of chief complaint of the patient. Another example, in respiratory symptoms, 'upper airway swelling' and 'sensation of throat closure' also confused. How to recognize 'Dizziness' followed by hypotension and 'Nausea' of Gastrointestinal symptom is also another example of the problem. Various situations that cannot be identified by algorithms are confusing the judgment of anaphylaxis at the vaccination center. Despite of this problem, it is a irony that the medical staffs in the vaccination center reports directly with filling the basic survey of anaphylaxis as the situation occurs. Not only that, It was impossible to check 'the laboratory results' (the result of mast-cell activation), 'capillary refill > 3 second', 'Reduced central pulse volume' in the vaccination center. Additional explanations for each items are needed for 2 reasons, (1) as to what each of these items means in the diagnosis of anaphylaxis (2) what should be measured for differential diagnosis. It is also necessary to reconsider whether the items presented in the algorithm should be placed in the criteria for judging anaphylaxis with the same weight as the symptoms immediately

identified in the field.

If information for the anaphylaxis diagnosis is supplemented, and tools are promoted and regular training is provided to medical staff facing patients in the field, confusion with differential diagnosis is also reduced, and misjudgment can be prevented. And the case of level 4 on BCCD caused by the lack of information will be decreased, it will be possible to secure more safety in the COVID-19 vaccination campaign.

Anaphylaxis research, especially anaphylaxis after vaccine is still insufficient. The most recent research of Anaphylaxis related to vaccination were in 2016. And due to the target of the vaccination campaign was mainly infants to adolescents, there have been few studies covering all ages through the country. In addition, the data source was the report of adverse event after vaccination in other previous anaphylaxis-related studies. And focused on only the epidemiological characters of the report, the clinical symptoms or characters of those were insufficient.

In this study, not only the demographic data but also the clinical symptom information could be obtained. With this, the correlation between selected risk factors and anaphylaxis incidence could be analyzed. In addition, the system that submit the medical records for diagnostic eligibility and causality evaluation of anaphylaxis, the biggest achievement was to examine the validity of Brighton Collaboration Case Definition, an diagnostic eligibility criteria, by reviewing the medical records of reported cases. Through these steps, the differences of clinical symptoms and chief complaints of the suspected anaphylaxis report case after the COVID-19 vaccination were found. Questions derived from those differences, the tools for

diagnostic eligibility could be rechecked by calculating sensitivity and specificity under the several conditions. Furthermore, it was possible to draw the ROC curve and calculate the AUC of BCCD. Finally, the validity of BCCD in Korea during COVID-19 vaccination campaign was examined.

Therefore, It is necessary to investigate other causes for the high report rate of suspected anaphylaxis. It is necessary to consider whether the description of the diagnostic eligibility criteria is well communicated to the medical staff and whether it is an environment in which the diagnostic eligibility criteria can be applied in the clinical field. With this study, it is hoped that this will relieve the public's anxiety about anaphylaxis after the COVID-19 vaccination, and contribute to the reduction of vaccine hesitancy not only in the COVID-19 vaccine but also in other Vaccine Preventable Diseases.

Reference

[1] Cardona V, Ansotegui IJ, Ebisawa M, El-Gamal Y, Fernandez Rivas M, Fineman S, Geller M, Gonzalez-Estrada A, Greenberger PA, Sanchez Borges M, Senna G, Sheikh A, Tanno LK, Thong BY, Turner PJ, Worm M. World allergy organization anaphylaxis guidance 2020. World Allergy Organ J. 2020 Oct 30;13(10):100472. doi: 10.1016/j.waojou.2020.100472. PMID: 33204386; PMCID: PMC7607509.

[2] Ahsan, Waquar, Nabeel K. Syed, Aseel A. Alsraeya, Hassan A. Alhazmi, Asim Najmi, Mohammed Al Bratty, Shamama Javed, Hafiz A. Makeen, Abdulkarim M. Meraya, Ahmed A. Albarraq, and Saad S. Alqahtani. 2021. 'Post-vaccination survey for monitoring the side effects associated with COVID-19 vaccines among healthcare professionals of Jazan province, Saudi Arabia', *Saudi medical journal*, 42: 1341-52.

[3] Almohaya, Abdulellah M., Farah Qari, Ghuzlan A. Zubaidi, Noura Alnajim, Khadeeja Moustafa, Malak M. Alshabi, Faleh M. Alsubaie, Ibrahim Almutairi, Qusai Alwazna, Jaffar A. Al-Tawfiq, and Mazin Barry. 2021. 'Early solicited adverse events following the BNT162b2 mRNA vaccination, a population survey from Saudi Arabia', *Prev Med Rep*, 24: 101595-95.

[4] Armstrong, Lisa, and Nicole Maguire. 2021. 'A Case Report of Prolonged Anaphylaxis after COVID-19 Vaccine'.

[5] Arnoldussen, D. L., M. Linehan, and A. Sheikh. 2011. 'BCG vaccination and allergy: a systematic review and meta-analysis', *J Allergy Clin Immunol*, 127: 246-53, 53.e1-21.

[6] Banerji, A., P. G. Wickner, R. Saff, C. A. Stone, Jr., L. B. Robinson, A. A. Long, A. R. Wolfson, P. Williams, D. A. Khan, E. Phillips, and K. G. Blumenthal. 2021. 'mRNA Vaccines to Prevent COVID-19 Disease and Reported Allergic Reactions: Current Evidence and Suggested Approach', *J Allergy Clin Immunol Pract*, 9: 1423-37.

[7] Bellomo, R. G., C. E. Gallenga, A. Caraffa, G. Tetè, G. Ronconi, and P. Conti. 2021. 'Anaphylaxis is a rare reaction in COVID-19 vaccination', *J Biol Regul Homeost Agents*, 35: 839-42.

[8] Cabanillas, B., and N. Novak. 2021. 'Allergy to COVID-19 vaccines: A current update', *Allergol Int*, 70: 313-18.

[9] Carvalho, J. C., F. Cunha, I. A. Coutinho, C. Loureiro, E. Faria, and A. T. Bom. 2021. 'Hypersensitivity Reactions to Vaccines: Current Evidence and Standards for SARS-CoV-2 Vaccines', *Acta Med Port*, 34: 541-47.

[10] Castells, M. C., and E. J. Phillips. 2021. 'Maintaining Safety with SARS-CoV-2 Vaccines', *N Engl J Med*, 384: 643-49.

[11] Castells, M., P. Demoly, and L. K. Tanno. 2021. '[Anaphylaxis and COVID-19 vaccines]', *Rev Fr Allergol (2009)*, 61: 8s30-8s35.

[12] Choe, Y. J., H. Lee, J. H. Kim, W. S. Choi, and J. Y. Shin. 2021. 'Anaphylaxis following vaccination among children in Asia: A large-linked database study', *Allergy*, 76: 1246-49.

[13] Chopard, D., M. S. Treder, P. Corcoran, N. Ahmed, C. Johnson, M. Busse, and I. Spasic. 2021. 'Text Mining of Adverse Events in Clinical Trials: Deep Learning Approach', *JMIR Med Inform*, 9: e28632.

[14] Dayneka, N., C. Jensen, and K. Hildebrand. 2020. 'Canadian

Immunization Guide: "Anaphylaxis and other acute reactions following vaccination" chapter update', *Can Commun Dis Rep*, 46: 384-86.

[15] de Silva, Debra, Chris Singh, Antonella Muraro, Margitta Worm, Cherry Alviani, Victoria Cardona, Auey DunnGlvin, Lene Heise Garvey, Carmen Riggioni, Elizabeth Angier, Stefania Arasi, Abdelouahab Bellou, Kirsten Beyer, Diola Bijlhout, M. Beatrice Bilo, Knut Brockow, Montserrat Fernandez-Rivas, Susanne Halken, Britt Jensen, Ekaterina Khaleva, Louise J. Michaelis, J. N. G. Oude Elberink, Lynne Regent, Angel Sanchez, Berber Vlieg-Boerstra, and Graham Roberts. 2021. 'Diagnosing, managing and preventing anaphylaxis: Systematic review', *Allergy*, 76: 1493-506.

[16] Demir, S., F. Erdenen, A. Gelincik, D. Unal, M. Olgac, R. Coskun, B. Colakoglu, and S. Buyukozturk. 2019. 'Evaluation of the Potential Risk Factors for Drug-Induced Anaphylaxis in Adult Patients', *Int Arch Allergy Immunol*, 178: 167-76.

[17] Desai, A. P., A. P. Desai, and G. J. Loomis. 2021. 'Relationship between pre-existing allergies and anaphylactic reactions post mRNA COVID-19 vaccine administration', *Vaccine*, 39: 4407-09.

[18] England, Public Health. 2013. *Vaccine safety and the management of adverse events following immunisation chapter 8*.

[19] Greenhawt, M., E. M. Abrams, J. Oppenheimer, T. K. Vander Leek, D. P. Mack, A. G. Singer, and M. Shaker. 2021. 'The COVID-19 Pandemic in 2021: Avoiding Overdiagnosis of Anaphylaxis Risk While Safely Vaccinating the World', *J Allergy Clin Immunol Pract*, 9: 1438-41.

[20] Grieco, Teresa, Patrizia Maddalena, Alvise Sernicola, Rovena Muharremi, Stefania Basili, Domenico Alvaro, Roberto Cangemi, Alfredo Rossi, and Giovanni Pellacani. 2021. 'Cutaneous adverse reactions after COVID 19 vaccines in a cohort of 2740 Italian subjects: An observational study', *Dermatol Ther*, 34: e15153-n/a.

[21] Hashimoto, Takanao, Akihiko Ozaki, Divya Bhandari, Toyoaki Sawano, Ranjit Sah, and Tetsuya Tanimoto. 2021. 'High anaphylaxis rates following vaccination with the Pfizer BNT162b2 mRNA vaccine against COVID-19 in Japanese healthcare workers: a secondary analysis of initial post-approval safety data', *Journal of travel medicine*, 28.

[22] Huh, K., Y. E. Kim, M. Radnaabaatar, D. H. Lee, D. W. Kim, S. A. Shin, and J. Jung. 2021. 'Estimating Baseline Incidence of Conditions Potentially Associated with Vaccine Adverse Events: a Call for Surveillance System Using the Korean National Health Insurance Claims Data', *J Korean Med Sci*, 36: e67.

[23] Jang, Gwang Cheon, Yoon-Seok Chang, Sun Hee Choi, Woo-Jung Song, Soo-Young Lee, Hae-Sim Park, Hye-Ryun Kang, Yeong-Min Ye, Hyun-Jung Jin, Mi Yong Shin, Soo-Jin Lee, Hye One Kim, Jihyun Kim, Jae-Woo Jung, Hee-Bom Moon, and Youngmin Ahn. 2013. 'Overview of anaphylaxis in Korea: diagnosis and management', *Allergy Asthma & Respiratory Disease*, 1.

[24] Jares, E. J., C. E. Baena-Cagnani, M. Sanchez-Borges, L. F. Ensina, A. Arias-Cruz, M. Gomez, M. N. Cuello, B. M. Morfin-Maciel, A. De Falco, S. Barayazarra, J. A. Bernstein, C. Serrano, S. Monsell, J. Schuhl, R. Cardona-Villa, and Group

Latin America Drug Allergy Interest. 2015. 'Drug-Induced Anaphylaxis in Latin American Countries', *J Allergy Clin Immunol Pract*, 3: 780-8.

[25] Jeong, K., Y. M. Ye, S. H. Kim, K. W. Kim, J. H. Kim, J. W. Kwon, S. I. Yang, S. Y. Lee, E. H. Chung, M. A. Kim, Y. H. Kim, H. Y. Kim, G. C. Jang, J. H. Kim, E. Lee, J. Kim, K. Ahn, Y. S. Chang, G. Y. Hur, J. Lee, T. K. Min, B. Y. Pyun, K. H. Park, J. Lee, T. W. Song, H. M. Jee, Y. S. Shin, D. Yoon, J. K. Lee, and S. Lee. 2020. 'A multicenter anaphylaxis registry in Korea: Clinical characteristics and acute treatment details from infants to older adults', *World Allergy Organ J*, 13: 100449.

[26] KDCA. 2021a. '주간 건강과 질병', *주간 건강과 질병*, 제14권 제15호.

[27] ---. 2021b. "코로나19 예방접종 후 이상반응 관리지침 2-1판 (22.2.16.)." In.

[28] ---. 2021c. "코로나19 예방접종 후 아나필락시스 판정 매뉴얼 (21.4.1.)." In.

[29] ---. 2022a. "코로나19 예방접종 후 이상반응 주간 분석 결과 52주차." In

[30] ---. 2022b. "60세 이상의 중증·사망 예방을 위해 4차접종 추진 (22.5.12.)." In

[31] ---. 2022c. "코로나19 예방접종 실시기준(22.2.14)." In.

[32] Kim, M. A., Y. W. Lee, S. R. Kim, J. H. Kim, T. K. Min, H. S. Park, M. Shin, Y. M. Ye, S. Lee, J. Lee, J. H. Choi, G. C. Jang, and Y. S. Chang. 2021. 'COVID-19 Vaccine-associated Anaphylaxis and Allergic Reactions: Consensus Statements of the KAAACI Urticaria/Angioedema/Anaphylaxis Working Group', *Allergy Asthma Immunol Res*, 13: 526-44.

[33] Klein, Nicola P., Ned Lewis, Kristin Goddard, Bruce Fireman, Ousseny Zerbo, Kayla E. Hanson, James G. Donahue, Elyse O. Kharbanda, Allison Naleway, Jennifer Clark Nelson, Stan Xu, W. Katherine Yih, Jason M. Glanz, Joshua T. B. Williams, Simon J. Hambidge, Bruno J. Lewin, Tom T. Shimabukuro, Frank DeStefano, and Eric S. Weintraub. 2021. 'Surveillance for Adverse Events After COVID-19 mRNA Vaccination', *JAMA*, 326: 1390-99.

[34] Kounis, N. G., I. Koniari, C. de Gregorio, D. Velissaris, K. Petalas, A. Brinia, S. F. Assimakopoulos, C. Gogos, S. N. Kouni, G. N. Kounis, G. Calogiuri, and M. Y. Hung. 2021. 'Allergic Reactions to Current Available COVID-19 Vaccinations: Pathophysiology, Causality, and Therapeutic Considerations', *Vaccines (Basel)*, 9.

[35] Laisuan, Wannada, Chamard Wongsa, Chirawat Chiewchalermsri, Torpong Thongngarm, Ticha Rerkpattanapipat, Pansa Iamrahong, Chulapha Ruangwattanachok, Sira Nanthapisal, and Mongkhon Sompornrattanaphan. 2021. 'Corona Vac COVID-19 Vaccine-Induced Anaphylaxis: Clinical Characteristics and Revaccination Outcomes', *Journal of asthma and allergy*, 14: 1209.

[36] Lee, E., Y. K. Lee, T. E. Kim, I. Hwang, Y. H. Jung, H. R. Lee, J. Song, Y. Park, E. Cho, and Y. K. Lee. 2021. 'Reports of anaphylaxis after coronavirus disease 2019 vaccination, South Korea, 26 February to 30 April 2021', *Euro Surveill*, 26.

[37] Lee, M. H., E. J. Roh, Y. M. Jung, Y. Ahn, and E. H. Chung. 2022. 'Characteristics of anaphylaxis patients who visited emergency departments in Korea: Results from a national

emergency department information system', *PLoS One*, 17: e0266712.

[38] Mikhail, Irene, David R. Stukus, and Benjamin T. Prince. 2021. 'Fatal Anaphylaxis: Epidemiology and Risk Factors', *Curr Allergy Asthma Rep*, 21: 28-28.

[39] Moghimi, S. Moein. 2021. 'Allergic Reactions and Anaphylaxis to LNP-Based COVID-19 Vaccines', *Mol Ther*, 29: 898-900.

[40] Perea-Valle, P., C. J. Delgado-Aguirre, B. G. Villafuerte-Domínguez, and B. E. Del Río-Navarro. 2022. '[Anaphylaxis caused by vaccines]', *Rev Alerg Mex*, 69 Suppl 1: s1-s14.

[41] Prevention, US Department of Health and Human Services/Centers for Disease Control and. 2020. 'Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of

[42] Pfizer-BioNTech COVID-19 Vaccine — United States, December 14 - 23, 2020', *MMWR*, Vol.70.

[43] ———. 2021. 'Allergic Reactions Including Anaphylaxis After Receipt of the

[44] First Dose of Moderna COVID-19 Vaccine — United States,

[45] December 21, 2020 - January 10, 2021', *MMWR*, Vol.70.

[46] Rasmussen, T. H., C. G. Mortz, T. K. Georgsen, H. M. Rasmussen, H. F. Kjaer, and C. Bindslev-Jensen. 2021. 'Patients with suspected allergic reactions to COVID-19 vaccines can be safely revaccinated after diagnostic work-up', *Clin Transl Allergy*, 11: e12044.

[47] Regateiro, F. S., M. L. Marques, and E. R. Gomes. 2020. 'Drug-Induced Anaphylaxis: An Update on Epidemiology and Risk Factors', *Int Arch Allergy Immunol*, 181: 481-87.

[48] Risma, Kimberly A. 2021. 'COVID-19 mRNA vaccine allergy', *Current opinion in pediatrics*, 33: 610-17.

[49] Roh, E. J., M. H. Lee, K. B. Song, Y. K. Lee, M. K. Kim, T. E. Kim, and E. H. Chung. 2020. 'Vaccine-related Anaphylaxis Cases Confirmed by KCDC from 2001-2016', *J Korean Med Sci*, 35: e337.

[50] Sa, S., C. W. Lee, S. R. Shim, H. Yoo, J. Choi, J. H. Kim, K. Lee, M. Hong, and H. W. Han. 2022. 'The Safety of mRNA-1273, BNT162b2 and JNJ-78436735 COVID-19 Vaccines: Safety Monitoring for Adverse Events Using Real-World Data', *Vaccines (Basel)*, 10.

[51] Sampath, V., G. Rabinowitz, M. Shah, S. Jain, Z. Diamant, M. Jesenak, R. Rabin, S. Vieths, I. Agache, M. Akdis, D. Barber, H. Breiteneder, S. Chinthrajah, T. Chivato, W. Collins, T. Eiwegger, K. Fast, W. Fokkens, R. E. O'Hehir, M. Ollert, L. O'Mahony, O. Palomares, O. Pfaar, C. Riggioni, M. H. Shamji, M. Sokolowska, M. Jose Torres, C. Traidl-Hoffmann, M. van Zelm, Y. Wang, L. Zhang, C. A. Akdis, and K. C. Nadeau. 2021. 'Vaccines and allergic reactions: The past, the current COVID-19 pandemic, and future perspectives', *Allergy*, 76: 1640-60.

[52] Shah, Ruchi H., Margaret M. Kuder, and David M. Lang. 2022. 'Anaphylaxis to Drugs, Biological Agents, and Vaccines', *Immunol Allergy Clin North Am*, 42: 121-44.

[53] Shaker, M. S., D. V. Wallace, D. B. K. Golden, J. Oppenheimer, J. A. Bernstein, R. L. Campbell, C. Dinakar, A. Ellis, M. Greenhawt, D. A. Khan, D. M. Lang, E. S. Lang, J. A. Lieberman, J. Portnoy, M. A. Rank, D. R. Stukus, J. Wang, Collaborators, N. Riblet, A. M. P. Bobrownicki, T. Bontrager,

J. Dusin, J. Foley, B. Frederick, E. Fregene, S. Hellerstedt, F. Hassan, K. Hess, C. Horner, K. Huntington, P. Kasireddy, D. Keeler, B. Kim, P. Lieberman, E. Lindhorst, F. McEnany, J. Milbank, H. Murphy, O. Pando, A. K. Patel, N. Ratliff, R. Rhodes, K. Robertson, H. Scott, A. Snell, R. Sullivan, V. Trivedi, A. Wickham, Editors Chief, M. S. Shaker, D. V. Wallace, Contributors Workgroup, M. S. Shaker, D. V. Wallace, J. A. Bernstein, R. L. Campbell, C. Dinakar, A. Ellis, D. B. K. Golden, M. Greenhawt, J. A. Lieberman, M. A. Rank, D. R. Stukus, J. Wang, Reviewers Joint Task Force on Practice Parameters, M. S. Shaker, D. V. Wallace, D. B. K. Golden, J. A. Bernstein, C. Dinakar, A. Ellis, M. Greenhawt, C. Horner, D. A. Khan, J. A. Lieberman, J. Oppenheimer, M. A. Rank, M. S. Shaker, D. R. Stukus, and J. Wang. 2020. 'Anaphylaxis-a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis', *J Allergy Clin Immunol*, 145: 1082-123.

[54] Shimabukuro, T. T., M. Cole, and J. R. Su. 2021. 'Reports of Anaphylaxis After Receipt of mRNA COVID-19 Vaccines in the US-December 14, 2020-January 18, 2021', *JAMA*, 325: 1101-02.

[55] Shimabukuro, Tom, and Narayan Nair. 2021. 'Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine.(Clinical Review & Education', *JAMA : the journal of the American Medical Association*, 325: 780.

[56] 'Singapore reviews safety of mRNA COVID-19 vaccine for people with anaphylaxis'. 2021. *BioSpectrum*.

[57] Sobczak, M., and R. Pawliczak. 2022. 'The risk of anaphylaxis behind authorized COVID-19 vaccines: a meta-analysis', *Clin Mol Allergy*, 20: 1.

[58] Su, J. R., P. L. Moro, C. S. Ng, P. W. Lewis, M. A. Said, and M. V. Cano. 2019. 'Anaphylaxis after vaccination reported to the Vaccine Adverse Event Reporting System, 1990-2016', *J Allergy Clin Immunol*, 143: 1465-73.

[59] Tanno, L. K., F. Berard, E. Beaudoin, A. Didier, and P. Demoly. 2021. 'SARS-CoV-2 Vaccination and Anaphylaxis: Recommendations of the French Allergy Community and the Montpellier World Health Organization Collaborating Center', *Vaccines (Basel)*, 9.

[60] Tanno, L. K., M. Castells, M. Caminati, G. Senna, and P. Demoly. 2021. 'Anaphylaxis and Coronavirus Disease 2019 vaccine: a danger relationship?', *Curr Opin Allergy Clin Immunol*, 21: 411-17.

[61] Tejedor-Alonso, M. A., E. Farias-Aquino, E. Pérez-Fernández, E. Grifol-Clar, M. Moro-Moro, and A. Rosado-Ingelmo. 2019. 'Relationship Between Anaphylaxis and Use of Beta-Blockers and Angiotensin-Converting Enzyme Inhibitors: A Systematic Review and Meta-Analysis of Observational Studies', *J Allergy Clin Immunol Pract*, 7: 879-97.e5.

[62] Turner, P. J., I. J. Ansotegui, D. E. Campbell, V. Cardona, M. Ebisawa, Y. El-Gamal, S. Fineman, M. Geller, A. Gonzalez-Estrada, P. A. Greenberger, A. S. Y. Leung, M. E. Levin, A. Muraro, M. Sánchez Borges, G. Senna, L. K. Tanno, B. Yu-Hor Thong, and M. Worm. 2021. 'COVID-19 vaccine-associated anaphylaxis: A statement of the World Allergy Organization Anaphylaxis Committee', *World Allergy*

Organ J, 14: 100517.

[63] Warren, C. M., T. T. Snow, A. S. Lee, M. M. Shah, A. Heider, A. Blomkalns, B. Betts, A. S. Buzzanco, J. Gonzalez, R. S. Chinthrajah, E. Do, I. Chang, D. Dunham, G. Lee, R. O'Hara, H. Park, M. H. Shamji, L. Schilling, S. B. Sindher, D. Sisodiya, E. Smith, M. Tsai, S. J. Galli, C. Akdis, and K. C. Nadeau. 2021. 'Assessment of Allergic and Anaphylactic Reactions to mRNA COVID-19 Vaccines With Confirmatory Testing in a US Regional Health System', *JAMA Netw Open*, 4: e2125524.

[64] Wieling, W., and H. Kaufmann. 2021. 'What is the best method to diagnose a vasovagal syncope?', *Clin Auton Res*, 31: 347-49.

[65] Worm, M., G. Sturm, J. Kleine-Tebbe, E. Cichocka-Jarosz, V. Cardona, I. Maris, and S. Dölle. 2017. 'New trends in anaphylaxis', *Allergo J Int*, 26: 295-300.

[66] Yacoub, M. R., V. Cucca, C. Asperti, G. A. Ramirez, E. Della-Torre, M. Moro, C. Zandalasini, D. Di Napoli, A. Ambrosio, C. Signorelli, S. Colombo, L. Beretta, F. Ciceri, A. Zangrillo, and L. Dagna. 2021. 'Efficacy of a rational algorithm to assess allergy risk in patients receiving the BNT162b2 vaccine', *Vaccine*.

[67] Muller MP, Tomlinson G, Marrie TJ, Tang P, McGeer A, Low DE, Detsky AS, Gold WL. Can routine laboratory tests discriminate between severe acute respiratory syndrome and other causes of community-acquired pneumonia? Clin Infect Dis. 2005 Apr 15;40(8):1079-86. doi: 10.1086/428577. Epub 2005 Mar 16. PMID: 15791504; PMCID: PMC7107805.

[68] Seo DH, Ye YM, Kim SC, Ban GY, Kim JH, Shin YS, et al.

A Single hospital survey of anaphylaxis in Korean adults : a multicenter retrospective case study. Allergy Asthma Immunol Res 2015;7:22-9

[69] Murad A, Katelaris CH. Anaphylaxis adult in a busy metropolitan Emergency Department : a review of real life management compared to best practice. Asia Pac Allergy 2026;6.29-34.

[70] Kim MY, Park CS, Jeong JW, Management and educational status of adult anaphylaxis patients at emergency department. Korean J Intern Med 2018; 33:1008-15.

Abstract

Epidemiologic characteristics of anaphylaxis reports after COVID-19 vaccination in Seoul, Korea

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Background

February 26, 2022 was the one-year of the start of the COVID-19 vaccination campaign in Korea. By February 26, 2022, Those who have completed 3rd vaccination following recommendation by the Korea Advisory Committee on Immunization Practice(KACIP) was 28,171,739, 55.4% of the total population in Korea. A total of 460,007 adverse events were reported. And 1,934 cases of suspected anaphylaxis were reported after COVID-19 vaccination, it was 1.63 cases per 100,000 doses. One of adverse events after vaccination was

anaphylaxis (including allergic reaction), which had a fatal trait that could be life-threatening in a short time. So the KACIP set anaphylaxis as Adverse Events of Special Interest(AESI) up to monitor recipients closely. In other countries, for example, 1.15 cases in Untied Kingdom, 0.36 cases in Germany, 1.52 cases in Japan were reported as anaphylaxis per 100,000 doses. Compared to those other countries, the incident rate of anaphylaxis after COVID-19 vaccination was relatively high in Korea. The problem is that anaphylaxis is affecting Vaccine hesitancy for people. Therefore, at this time, which is the first year of starting the COVID-19 vaccination campaign in Korea, tried to find out the epidemiological characteristics of the reported cases of suspected anaphylaxis (including allergic reaction) and to review the Seoul's cases in which causality was confirmed as anaphylaxis by measuring the validity of the Brighton Collaboration Case Definition(BCCD), a criteria for evaluating diagnostic eligibility.

Methods

The demographic characteristics and clinical symptoms of cases reported as 'Anaphylaxis' or 'Suspected anaphylaxis' to KDCA system for surveillance the AEFIs in korea were analyzed. Data collecting period was from February 26. 2021. to February 26, 2022. Based on the analysis data, choosing some risk factors (in this study, these were sex, age, vaccine type and the past history of allergic reaction history) that might be related to the incidence of anaphylaxis following COVID-19 vaccination found out the correlation by multiple regression analysis. Sensitivity and specificity of BCCD were calculated and then measured the validity of BCCD. Finally, reasons

for the high reporting rate compared to other countries that implement COVID-19 vaccination were investigated.

Results

A total of 1,934 cases of suspected anaphylaxis were reported after COVID-19 vaccination in Korea, 841 cases were confirmed by the evaluation of eligibility for diagnosis and evaluation of the causality by the BCCD. For every 100,000 doses, 1.63 cases were reported and 0.71 cases were confirmed the causality in Korea. During the same period, in Seoul, there was a total of 534 reports of suspected anaphylaxis after COVID-19 vaccination and 145 cases were confirmed the causality as the same way. 0.44 cases were reported and 0.12 cases were confirmed the causality per 100,000 doses.

The demographic characteristics of suspected anaphylaxis report after COVID-19 vaccination in Seoul were that women 71.7%, 20-29 years 26.8%, Pfizer-vaccine recipients 73.8%, had the past history of allergic reaction related drug/food 77.5% took the part in total (total = 534 cases).

Clinical symptoms in the confirmed cases of Seoul were observed 'suddenly' and 'rapidly' at the most of cases (except 1 case didn't satisfy the 'rapidly' but confirmed as a delayed anaphylaxis symptom.) and Respiratory symptom was observed in 72.9% of reported cases, followed by Cardiovascular (51.5%), Cutaneous symptom (32.9%), Gastrointestinal (25.3%) symptoms. The most of confirmed cases of symptom onset time was <15 minutes. There is no case of containing laboratory results, Epinephrine injection (64.1%) is the most common treatment, followed by antihistamine (49.7%),

corticosteroids (41.4%), and applying oxygen (20.0%).

Based on this results, the next step was necessary in order to find out the reason why the incidence rate of suspected anaphylaxis cases was increased. Risk factors estimated to be related to the occurrence of anaphylaxis were selected. These were Age, Sex, Vaccine types, the past history of allergy reactions for drugs or foods of recipients.

A total of 534 cases of suspected anaphylaxis were reported after the COVID-19 vaccination in Seoul during study period. Among them, group 'Anaphylaxis' that were confirmed diagnostic eligibility and causality were 145 cases, group 'Not anaphylaxis' were 340 cases. 11 cases where causality results were not reported were excluded. In the group 'Anaphylaxis', the percentage of each risk factor was as follows. In case of sex, men 26.9%, women 73.1%. The median age was 34 years old (SD : ±15.55 years). The vaccine types, Pfizer 75.2%, Astrazeneka and Morderna 8.9%, Janssen 7.0% took the part respectively. Those who had 'the past history of allergic reactions related drug/food ' were 42.8%, and those who didn't have were 57.2%. The mean onset time was 82.82 minutes (SE : ±18.47 min). With these risk factors, the Odds ratios were calculated by Chi-square test. As a result, there was a difference depending on the type of vaccine, and the Odds ratio was confirmed to be 2.78 in the recipients who had the past history of allergic reaction related to food/drug.

Unlike previous studies, to confirm the possibility that the tools used to evaluate diagnostic eligibility and causality may have affected the increased incidence rate of suspected anaphylaxis cases after

COVID-19 vaccination, the validity of BCCD was measured. The report data for suspected anaphylaxis and the evaluation result of diagnostic eligibility were placed as predicted values and diagnostic results, respectively. The result was that sensitivity 26%, specificity 33% and AUC was 0.73 by ROC curve. The validity of BCCD in Korea is 'Fair' according to Muller's criteria. ($0.7 \leq AUC < 0.8$)

Conclusion

There were two differences from the results of previous anaphylaxis studies related to vaccination conducted in Korea.

First, the incidence rate of anaphylaxis and the number of cases that were confirmed casuality after COVID-19 vaccination were different. The incidence of vaccine-related anaphylaxis has been reported very little, the incidence rates of vaccine-related anaphylaxis per million dose was 0.090 in 2005, 0.079 in 2012, 0.071 in 2013, 0.188 in 2015, 0.036 in 2016. The causality confirmed cases were 13 in total from 2001 to 2016. However, for every 100,000 doses, 1.63 cases were reported and 0.71 cases were confirmed the causality in Korea during COVID-19 vaccination campaign. There were differences in both the suspected anaphylaxis report rate related to vaccination before and after COVID-19 vaccination. And the confirmed anaphylaxis cases after COVID-19 vaccination, it increased in COVID-19 vaccination.

Secondly, There were differences in major clinical symptoms of anaphylaxis after the vaccination. In previous study about epidemiology of anaphylaxis, clinical symptoms of drug-induced anaphylaxis were as follows. Cutaneous/mucosal symptoms (itching, urticaria etc.) took part of 80-90%, respiratory symptoms were 70%,

gastrointestinal symptoms were 30-45%, cardiovascular symptoms were 10-48%, neurology symptoms 10-15% of patients. In this study, clinical symptoms of the confirmed anaphylaxis cases after COVID-19 vaccination were respiratory symptoms 72.9%, cardiovascular symptoms 51.5%, cutaneous/mucosal symptoms 32.9%, gastrointestinal symptoms 25.3% were followed.

Since the validity of the Brighton Collaboration Case Definition, a criteria for evaluating eligibility for diagnosis, was confirmed to be 'Fair', it is necessary to investigate other causes about the high report rate of suspected anaphylaxis. With this study, it is hoped that this will relieve the public's anxiety about anaphylaxis after the COVID-19 vaccination, and contribute to the reduction of vaccine hesitancy not only in the COVID-19 but also in other Vaccine Preventable Diseases.

keywords : COVID-19 Vaccine, Vaccine-related Anaphylaxis, Anaphylaxis, Adverse events following immunization, Epidemiologic characters of anaphylaxis
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