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Antibiotic use in elderly patients in ambulatory care: A comparison between Hungary and Sweden

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Background: The elderly use antibiotics frequently due to their increasing infection susceptibility. Given the high and increasing proportion of elderly in the population, their antibiotic use is substantial. *Objective:* This study aimed to compare antibiotic use in the elderly in the ambulatory care sector between Hungary and Sweden.

Methods: This retrospective, descriptive, cross-national, comparative study included antibacterial use data from the Hungarian National Health Insurance Fund and the Swedish eHealth Agency. Antibiotic use (anatomical therapeutical chemical: J01) was expressed as the number of prescriptions/1000 inhabitants/year or month and was further stratified by age and sex.

Results: Antibiotic exposure was higher in the Hungarian elderly population (649.8 prescriptions/1000 inhabitants/year) compared to its Swedish counterparts (545.0 prescriptions/1000 inhabitants/year). Hungary had a similar scale of antibacterial exposure across all elderly age subgroups, with different trends in males and females, while Sweden had a stepwise increase in antibiotic exposure by age in both sexes. The seasonal fluctuation was high in Hungary and reached a peak of 80.7 prescriptions/1000 inhabitants/month in January 2017, while even antibiotic use was detected throughout the year in Sweden. The pattern of antibiotic use in the elderly considerably differed between the two countries. Penicillin and beta-lactamase combinations, such as co-amoxiclav, were more frequently used in Hungary than in Sweden (19.08% vs 1.83% of corresponding total ambulatory antibiotic use). Likewise, quinolones were more commonly used in Hungary than in Sweden (34.53% vs. 9.98). The elderly in Sweden were mostly prescribed narrow spectra penicillins (26.71% vs. 0.29% in Hungary).

Conclusion: This cross-national comparison revealed important differences in all aspects of antibiotic use in the elderly between the two countries. The identical scale and pattern of antibiotic use cannot be anticipated due to the poorer health status of the Hungarian elderly population. However, the substantial differences indicate some room for improvement in the antibiotic prescription for the Hungarian elderly.

KEYWORDS

drug utilization study, ambulatory care, antibacterials, elderly, cross national comparison, prescrptions/1000 inhabitants/year, public health, antibiotic stewardship

Introduction

Antimicrobial resistance (AMR) implies a threat to global human health. Contributing factors of AMR include antibiotic overuse and misuse in hospital and ambulatory care settings (Ventola, 2015). Current demographic projections show an increasing elderly population in Europe. In 2019, proportion of the elderly population (≥65 years) proportion in Europe, Hungary, and Sweden was 31.4%, 29.3%, and 31.9%, respectively, of the total adult active (15–64 years) population, which is projected as 39.1%, 33.7%, and 34.4% by 2030, respectively (Eurostat, 2019).

The elderly population is at increased risk of many infectious diseases due to progressive functional decline of the immune system, commonly referred to as immunosenescence (Feehan et al., 2021). Age-related immune system changes affect innate and adaptive immune responses (Feehan et al., 2021). Research data on outpatient antibiotic use in the elderly remained scarce despite the growing population size of the elderly in Europe, and most studies focus on long-term care facilities (Raban et al., 2021). Comprehensive country-wide data on antibiotic use in the elderly in ambulatory care have only been published for a limited number of countries, including Denmark (Jensen et al., 2021), Norway (Blix et al., 2007), and the United States (Kabbani et al., 2018). Moreover, no cross-national comparison research has compared antibiotic use for the elderly in ambulatory care between European countries. Therefore, this study aimed to compare antibiotic use in the elderly in the ambulatory care sector in Hungary and Sweden.

Methodology

Study design and setting

This retrospective and descriptive cross-national comparative study collected data on antibacterial prescriptions dispensed at community pharmacies in Hungary and Sweden in 2017. Antibacterials were classified according to the anatomical therapeutical chemical (ATC) classification system defined by the World Health Organization (WHO), version 2022 (WHO, 2020). The use of systemic antibacterials (ATC: J01) was measured as prescriptions/1000 inhabitants/year or month. The elderly population (aged >65 years) of Hungary and Sweden in 2017 served as study populations for this study, including 1,828,226 elderly in Hungary and 1,976,857 elderly in Sweden (data derived from Eurostat). The two populations were further stratified into subgroups according to age (65–69 years, 70–74 years, 75–79 years, 80–85 years, and >85 years) and sex. Seasonal variation of antibiotic consumption was also assessed.

Description of databases

Data on antibacterial use was obtained from the Hungarian National Health Insurance Fund and the Swedish eHealth Agency. Both the Hungarian and the Swedish national health insurance systems cover almost 100% of the population of each country. The database in Hungary contains records of all dispensed and reimbursed ambulatory care prescriptions issued by general practitioners (GPs), specialists, and dentists to ambulatory care patients, nursing home residents, and patients visiting private practices (e.g., gynecologists, dentists). The drug coverage is approximately 95% because non-reimbursed antibiotics are not included in the database.

The Swedish database contains data on all dispensed antibiotic prescriptions providing 100% drug coverage. All medications prescribed to outpatients (irrespective of reimbursement status) that are issued by GPs, specialists, dentists, patients visiting private practices, or nursing homes are included in this database.

Statistics

Excel was used for the statistical analyses, and visualization was done by the R package (version 4.1.2).

Ethical considerations

Ethical approval was not needed because aggregated data were collected for both countries.

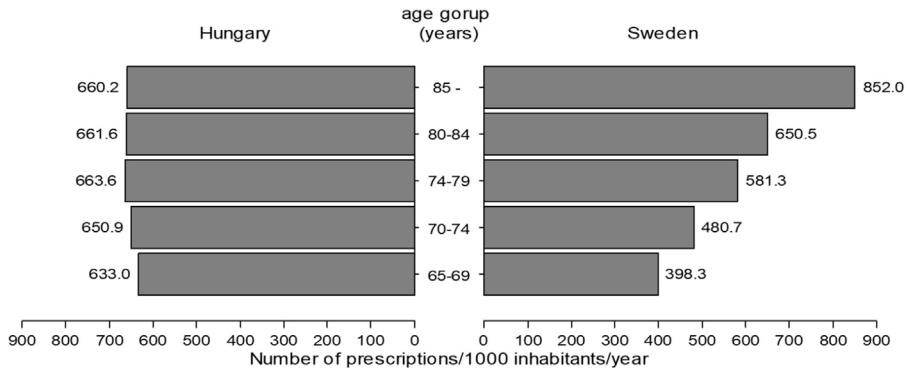

FIGURE 1
Antibacterial use in different elderly age subgroups in Hungary and Sweden (2017).

Results

The scale of antibiotic use

The entire Hungarian population (approximately 9.8 million people) was dispensed 6,792,714 prescriptions of antibiotics in 2017, 17.5% of which were dispensed to the elderly. Concurrently, the entire Swedish population (approximately 10 million people) was dispensed 3,204,838 prescriptions of antibiotics, 33.6% of which were dispensed to the elderly. The antibiotic exposure was 649.8 prescriptions/1000 inhabitants/year in Hungarian and 545.0 prescriptions/1000 inhabitants/year in the Swedish elderly population.

Figure 1 presents the level of antibiotic exposure across the elderly age subgroups. The antibacterial exposure of the Hungarian elderly population was similar across all age subgroups, while a stepwise increase was observed in antibacterial exposure by age subgroups (an increase from 398 [65–69 years old] to 852 (>85 years old) prescriptions/1000 inhabitants/year) in the Swedish elderly population.

The pattern of antibiotic use

Table 1 shows the absolute and relative use of different antibacterial subgroups. Concerning the beta-lactam antibacterials, the penicillin group in Hungary was responsible for one-fifth of total ambulatory care antibiotic use in the elderly, and cephalosporins also had considerable use and share. In contrast, the penicillin group in Sweden was responsible for almost half of antibiotic use in the elderly, and marginal cephalosporin use was observed. The absolute and relative use of macrolides and fluoroquinolones were considerably higher in the Hungarian elderly population than in the Swedish counterparts, with an opposite pattern for tetracyclines and other antibacterials because their use was higher in the Swedish elderly (Table 1).

Table 2 shows the top ten list of antibacterials. Amoxicillin and clavulanic acid (co-amoxiclav) and two fluoroquinolones (levofloxacin and ciprofloxacin) covered almost half (46.6%) of the antibiotic use of the Hungarian elderly population in ambulatory care (Table 2), whereas 40% of all antibiotics used by the elderly population in ambulatory care constituted of the narrow-spectrum penicillin V, flucloxacillin, or pivmecillinam in Sweden. Nitrofurantoin use was almost absent in Hungary but constituted approximately 10.5% of the elderly antibiotic use in Sweden.

Sex-specific antibiotic use

Overall, elderly females used more antibiotics than elderly males in Hungary and Sweden. Elderly females have been exposed to antibiotics at 668 prescriptions/1000 elderly females/year in Hungary, while elderly males at 620 prescriptions/1000 elderly males/year. Swedish elderly females were exposed to antibiotics at 618 prescriptions/1000 females/year, while elderly males at 460 prescriptions/1000 males/year in ambulatory care.

However, the antibiotic exposure of the two sexes of the elderly population showed opposite trends in the age subgroup analysis in Hungary (Figure 2). Antibiotic use decreased from 685 prescriptions/1000 females/year (60–65 years old) to 631 prescriptions/1000 females/year (>85 years old) in Hungary. Conversely, the scale of antibiotic use in the Hungarian elderly male increased by age [from 563 prescriptions/1000 males/year (65–69 years old) to 739 prescriptions/1000 males/year (>85 years old)]. Both elderly females and males in Sweden were exposed to increasing amounts of antibiotics by increasing age (Figures 1, 2) and in all elderly subgroups Swedish females were exposed to more antibiotics than Swedish males).

Seasonal variation

Figure 3 shows the seasonal variation in antibiotic use in the elderly in Hungary and Sweden. The seasonal fluctuation was high in Hungary, reaching a peak of 80.7 prescriptions/1000 inhabitants/

TABLE 1 Absolute and relative use of different antibiotic subgroups in the elderly population in Hungary and Sweden.

	Hungary	Sweden
J01A Tetracyclines	15.46 (2.38%)	52.84 (9.7%)
J01C Beta-lactam antibacterials, penicillins	141 (21.7%)	260.53 (47.81%)
J01CA Penicillins with extended spectrum	15.12 (2.33%)	105.03 (19.27%)
J01CE-CF Narrow-spectrum penicillins	1.90 (0.29%)	145.55 (26.71%)
J01CR Penicillin combinations, including beta-lactamase inhibitors	123.99 (19.08%)	9.96 (1.83%)
J01D Other beta-lactam antibacterials	75.45 (11.61%)	9.14 (1.68%)
J01DB First-generation cephalosporins	0.60 (0.09%)	8.79 (1.61%)
J01DC Second-generation cephalosporins	58.36 (8.98%)	0.01 (>0.01%)
J01DD Third-generation cephalosporins	16.49 (2.54%)	0.26 (0.05%)
J01E Sulfonamides and trimethoprim	36.18 (5.57%)	28.56 (5.24%)
J01EA Trimethoprim and derivatives	-	13.93 (2.56%)
J01EE Combinations of sulfonamides and trimethoprim, incl. derivatives	36.18 (5.57%)	14.63 (2.68%)
J01F Macrolides, lincosamides, and streptogramins	120.06 (18.48%)	32.41 (5.95%)
J01FA Macrolides	82.86 (12.75%)	8.41 (1.54%)
J01FF Lincosamides	37.20 (5.72%)	24.00 (4.4%)
J01M Quinolones	224.38 (34.53%)	54.41 (9.98%)
J01X Other antibacterials	36.17 (5.57%)	106.96 (19.63%)
J01XE Nitrofuran derivatives	0.02 (>0.01%)	57.17 (10.49%)
J01XX Other antibacterials (e.g., fosfomycin, methenamine)	36.12 (5.56%)	49.09 (9.01%)
Other	1.11 (0.17%)	0.11 (0.02%)
Total (J01)	649.81 (100%)	544.96 (100%)

Unit = Prescriptions/1000 inhabitants/year.

month in January. The lowest value in Hungary was 39.2 prescriptions/1000 inhabitants/month in July. Antibacterial use in the elderly population in Sweden was more equally distributed over the entire year, with a peak consumption of 49 prescriptions/1000 inhabitants/month in March and a nadir of 42 prescriptions/1000 inhabitants/month in April.

Discussion

To the best of our knowledge, this is the first study to report on Hungarian data on antibiotic use in the elderly and the first age-specific comparison of antibiotic use between two countries. Our results showed that antibiotic exposure was higher in the Hungarian elderly population than in their Swedish counterparts. Several factors might explain the higher antibiotic exposure in the Hungarian elderly than in Sweden.

Scale of use

Life expectancy is one of the most commonly used measures of the overall health of a population. The average life expectancy in 2017 for those aged 65 years was higher in Sweden than in Hungary (20.40 years vs 16.70 years), meaning that the Hungarian elderly has poorer health status (Eurostat, 2022).

Data on acute infection incidences are unavailable in the national statistics, but data on chronic disease prevalence, which can increase infection risk compared to the healthy population, is retrievable and can partly explain the observed differences between Hungary and Sweden. Two-thirds of Hungarians and nearly half of Swedish elderly (aged ≥65) reported at least one chronic disease (OECD, 2020). An epidemiological research revealed that patients with diabetes suffer infections more frequently than those without diabetes with consequent higher antibiotic use (Alves et al., 2012). The prevalence of diabetes in the elderly was higher in 2014 in Hungary than in Sweden (18.6% vs 12.6%) (Eurostat, 2014c). Obesity has also been an independent risk factor for infections in retrospective and prospective studies (Harpsøe et al., 2016). It increases the risk of pneumococcal respiratory tract infections (RTI), skin, gastrointestinal tract, and urinary tract infections (UTI) in elderly individuals (Frasca and McElhaney, 2019; Ghilotti et al., 2019). The prevalence of obesity in the elderly was much higher in 2014 in Hungary than in Sweden (26.5% vs 14.5%) (Eurostat, 2014a).

Smoking is one of the main risk factors for RTI, and the rate of daily smokers among the elderly was higher in Hungary (10.8%) than in Sweden (7.2 %), however this difference is much higher in the overall population (28 % vs. 7%, in 2020).

TABLE 2 The top ten list of antibacterials used in the elderly population in Hungary and Sweden (2017).

Hungary	Prescriptions/ 1000 inhabitants/year	Percentage	Sweden	Prescriptions/ 1000 inhabitants/year	Percentage
co-amoxiclav	123	18.95	phenoxymethylpenicillin	81.5	14.95
levofloxacin	95.8	14.75	pivmecillinam	72.3	13.27
ciprofloxacin	83.9	12.92	flucloxacillin	64.0	11.75
azitromycin	57.1	8.78	nitrofurantoin	57.2	10.49
cefuroxim	48.2	7.42	ciprofloxacin	52.8	9.68
clindamycin	37.2	5.72	methenamine	48.5	8.90
sulfamethoxazole/ trimethoprim	36.2	5.57	doxycycline	47.9	8.80
fosfomycin	36.1	5.56	amoxicillin	32.7	6.00
norfloxacin	24.5	3.78	clindamycin	24.0	4.40
clarithromycin	23.3	3.59	SMX/TMP*	14.6	2.68

*SMX/TMP, sulfamethoxazole and trimethoprim.

In addition, smoking increases infection risk for digestive, reproductive, and other systems, which could lead to slightly higher antibiotic use in Hungarian elderly than in Swedish (Jiang et al., 2020). The annual number of hospital discharges due to malignant neoplasm of the respiratory tract (trachea, bronchus, and lung) in 2017 was also higher in Hungarian elderly (13,115 patients) than in its Swedish counterparts (4,966 patients) (Eurostat, 2017a). Prescribers may have a lower threshold for initiating antibiotic use in patients with cancer because antibiotics have positive side effects, such as cancer apoptosis promotion, cancer growth inhibition, and cancer metastasis prevention, e.g., lung cancer (Gao et al., 2020).

The population's low health literacy and health-related knowledge can contribute to patients' attitudes, beliefs, perceptions, and behaviors related to antibiotic use and can result in higher overall antibiotic use (Salm et al., 2018). The Eurobarometer public survey from 2018 revealed that the Hungarian public's knowledge of antibiotics was worse than Swedish because only 37% of respondents gave entirely correct answers for all four antibiotic knowledge-related questions in Hungary, while 74% in Sweden (WHO, 2018).

The Eurostat statistics from 2017 revealed that the proportion of Hungarian elderly with >10 GP visits per year was 20.0% (65–74 years) and 29.5% (≥75 years), while this rate was only 3.7% (65–74 years) and 5.8% (≥75 years or more) in Sweden, suggesting that GP visits have a lower threshold in the Hungarian elderly population, which can contribute to higher antibiotic use (Tyrstrup et al., 2017). In addition, of the surveyed people in Hungary in the Eurobarometer study, 25% stated antibiotic prescription for sore throat and 17% for fever, while 9% for sore throat and 2% for fever in Sweden (European Commission, 2016). Data suggests that initiating antibiotic treatment is less judicious among Hungarian doctors although this data is based on patient recalls. Misleading advertising can be partly responsible for this. Over-the-counter dorithricin-containing lozenges, a local antibiotic, were heavily advertised on TV as a "throat saver antibiotic" in earlier years in Hungary, sending the incorrect message both to patients and doctors that antibiotics are required to relieve sore throats.

Physicians are primarily responsible for the decision to use antibiotics; thus, ensuring the optimal attitudes and knowledge that underlie their prescribing habits is a prerequisite for improving prescription quality (Gonzalez et al., 2015). A recent study revealed a 20% proportion of final-year medical students who want more education on prudent antibiotic use in Sweden, while >71% in Hungary. This means that medical students in Sweden feel prepared for prudent antibiotic prescription in much higher percentages than final-year students in Hungary (Dyar et al., 2018).

Moreover, antibiotic use is influenced by the existence of a national antibiotic policy (WHO, 2011). Sweden implemented the WHO recommendations for antibiotic stewardship in the form of a national strategic program to combat antibiotic resistance (Medical Products Agency and Strama, 2008), which is a continuously evolving collaboration that has been in place since 1995 (Mölstad et al., 2017). In contrast, a national antibiotic policy is not implemented with clear targets, responsibilities, and dedicated funding in Hungary (WHO, 2018).

Market forces and manufacturers' marketing activity can also largely influence prescription practices in Hungary (WHO, 2018). The number of generics is very high in Hungary because they aim to reduce the price as much as possible (MacKenzie et al., 2006; Wouters et al., 2017), which might promote higher antibiotic use.

Overall, our study revealed that elderly females were prescribed more antibiotics than males in both

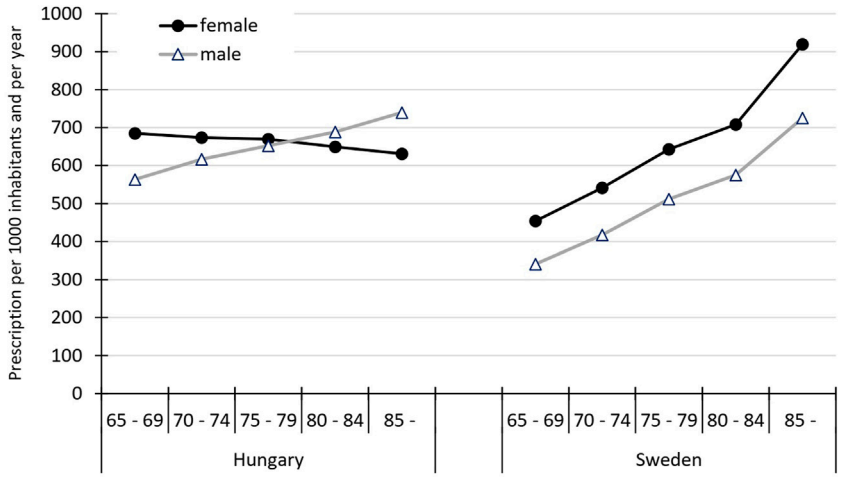

FIGURE 2
Sex-specific use of antibiotics in ambulatory care presented by age subgroups in the elderly population in Hungary and Sweden (2017).

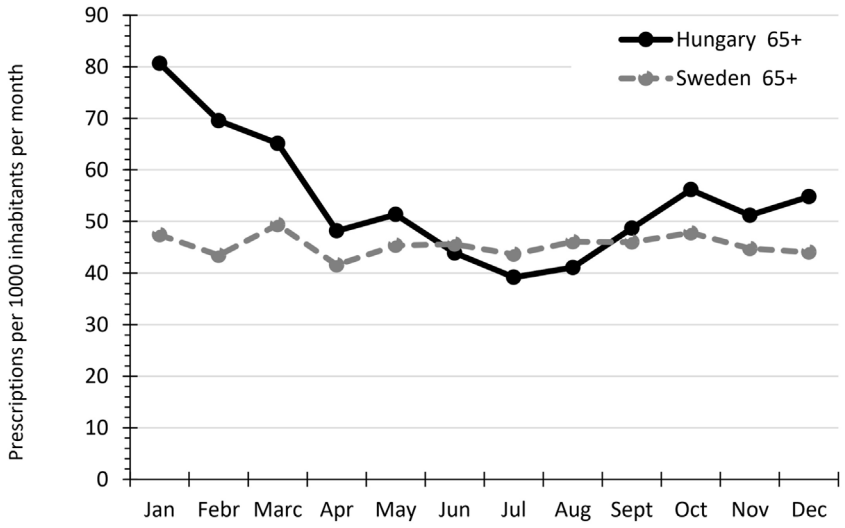

FIGURE 3
Seasonal variation of antibiotic use among the elderly population in Hungary and Sweden in 2017.

countries. This can be partly explained by the sex differences in GPs visiting rates, wherein the rate of Hungarian elderly with >10 GP visits per year was 17.7% and 28.6% for males aged 65–74 years and >75 years, respectively, while 21.5% and 30.0% in the same age groups for females.

The sex gap in antibiotic prescription can partly be explained by consultation behavior differences (Smith et al., 2018). Males and females communicate differently with healthcare professionals, and prescribers may have gender biases that affect their willingness to prescribe antibiotics, resulting in higher antibiotic use in females (Smith et al., 2018). Males in the oldest two age groups were prescribed more antibiotics in Hungary due to the higher prevalence of risk factors among males, such as smoking and excessive alcohol consumption (WHO, 2018). The number of elderly male smokers is double compared to elderly female smokers aged 65–74 years and is five times higher in >75 years old in Hungary. Meanwhile, both sexes are equally smokers in each age subgroup in Sweden (Eurostat, 2014).

Pattern of use

We found that the absolute and relative ambulatory care use of different antibacterial subgroups differed greatly in the elderly population between Hungary and Sweden. In Hungary, penicillin beta-lactamase combinations, such as co-amoxiclav were preferred, compared to Sweden where it was marginally used (19.08% vs 1.83%). The high use of co-amoxiclav has been estabilished in previous research as a drug of choice for RTI in Hungary (Matuz et al., 2013). Swedish policy recommends prescribing narrow-spectrum penicillins in ambulatory care for RTI (Aspevall et al., 2020) and our data indirectly indicate good adherence to this guideline. Surveillance report from the European Antimicrobial Resistance Surveillance Network (EARS-Net) showed that percentages of penicillin-resistant pneumococci (PRP) were similar in Hungary (6.9%) and Sweden (6.1%) (ECDC, 2017). Clavulanic acid use is not necessary for PRP because the resistance mechanism is not connected to the bacteria's capability to produce beta-lactamase enzymes; hence, the addition of clavulanic acid to aminopenicillin will not help to overcome this resistance (Huttner et al., 2020). Co-amoxiclav is dominantly used compared to amoxicillin alone in Hungary because co-amoxiclav was placed on the market earlier than amoxicillin alone; thus, doctors became used to it (Benko, 2016). The use of broad-spectrum antibiotics, such as co-amoxiclav can compromise the host microbiome. Even short-term antibiotic exposure alters the gut microbiota and bacterial diversity recover after weeks or months after (Elvers et al., 2020). Disruption of the human microbiom by antibiotic use can lead to AMR infections and several diseases such as allergia, asthma, obesity or vitamin K deficiency (Langdon et al., 2016).

Quinolone was also more frequently used in Hungary than in Sweden (34.53% vs. 9.98% of total ambulatory use in the elderly, respectively). Previous research showed that fluoroquinolones were commonly used in ambulatory care to treat urinary tract infections and also RTIs in Hungary (Juhasz et al., 2013; Matuz et al., 2015; Benkő et al., 2020). Contrarily, pivmecillinam and nitrofurantoin were proved to be the first-line antibiotics to treat community-acquired UTIs in Sweden (Kornfält et al., 2019). The consequences of high fluoroquinolone use can be various. The Food and Drug Administration has placed a boxed warning on fluoroquinolone antibiotics which highlights older adults as being at an elevated risk of serious side effects, including tendon rupture, delirium, peripheral neuropathy, blood sugar disturbances, and aortic dissection (U.S. Food and Drug Administration, 2018). Fluoroquinolones also increase the risk of CDI (*Clostridioides difficile* infection) (Kabbani et al., 2018). Fluoroquinolone can cause QT interval prolongation and subsequently increase the risk of *torsades de pointes (TdP) type arrhythmias*. Given that heart failure and other risk factors such as uncorrected hypokalaemia, hypomagnesaemia might be present more frequently in the elderly, they are more vulnerable to potentially fatal cardiac arrhythmias such as TdP (Stahlmann & Lode, 2010). The 2017 annual report of the EARS-Net showed a difference in the percentage of fluoroquinolone-resistant *Escherichia coli* between Hungary and Sweden (30.6% vs 15.8%, respectively) that could be due to differences in the quinolone use in the two countries (ECDC, 2017).

The results of this comparison between the two countries are essential for Hungary since they need to optimize antibiotic use in the elderly to prevent serious adverse effects, more rapid resistance development, and higher costs (WHO, 2018). The availability of therapeutic guidelines might contribute to the observed pattern of antibiotic use in both countries. Up-to-date diagnostic and treatment guidelines have been unavailable for most community-associated infections for several years in Hungary, but Sweden continuously updates the guidelines every 3 years (Government Offices of Sweden, 2020).

Seasonal antibiotic use

The Hungarian antibiotic use in the elderly was very similar to Sweden in the summer months, but we detected substantially higher antibiotic use in the Hungarian elderly in the winter months. Seasonal fluctuation of outpatient antibiotic use in the general population across European countries has been previously described (Elseviers et al., 2007) and linked to an increased prevalence of RTI during the winter months, resulting in higher antibiotic prescription rates during this time (Elseviers et al., 2007).

Viral RTI and influenza-like syndromes were the most frequent infections in winter in both countries (Folkhälsomyndigheten, 2017; Kovács and Pakot, 2020); thus, antibiotics were possibly prescribed for self-limiting viral infections. The close correlation between viral respiratory infections, such as influenza and antibiotic prescriptions (Ryu et al., 2018), suggests that reducing the incidence of influenza through vaccination efforts in elderly people (Smetana et al., 2018) could help decrease the overprescription of antibiotics. The Eurostat in 2017 reported that Sweden has a higher vaccination rate against influenza in the population aged ≥65 years (49.8%) than in Hungary (26.8%) (Eurostat, 2017b), which might result in lower influenza illness rates in Sweden.

Study strengths and limitations

The strength of this study is the nearly 100% population and drug coverage in both countries. However, some limitations need to be acknowledged. Firstly, this research only uses 1-year data from the two countries, which precludes analysis of annual trends in antibiotic use. Secondly, data is not stratified by specific indications. However, these limitations do not affect our aims and conclusions. Finally, we have to highlight, that systemic antibiotic use (WHO: J01) includes methenamine (urinary disinfectant) with considerable use in Sweden (sixth place on the top list). Excluding methenamine would result in even higher differences in the antibiotic utilization of the two countries.

Conclusion

The scale and pattern of elderly ambulatory antibiotic use differed between Hungary and Sweden. Some of the observed differences could be explained by the different health statuses between the two populations; however, data suggest that interventions are needed to optimize antibiotic use in the elderly in Hungary.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Aggregated datasets (without age, gender) is publicly available, while more detailed should be requested from the National Health Fund (NEAK). Requests to access these datasets should be directed to www.neak.gov.hu.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conceptualization: MM, RB, MH, IK, RB; methodology, formal analysis, software, RB and MM; investigation, RB and MM, data curation, validation, MH, EH, and AV; writing—original draft preparation, IK; writing—review and editing, IK, MM, RB, and MB; and funding acquisition, DC. writing: RB, RR, IK, writing, review, editing: MM, RB, EH, ÁV, PD, MB, EZ, DC. All authors have read and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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RESEARCH ARTICLE

Antibiotic knowledge assessment questionnaire in undergraduate pharmacy students: A Rasch analysis of validity evidence

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Abstract

Background: Antibiotic knowledge is crucial for undergraduate pharmacy students who are future healthcare professionals. However, a valid and reliable instrument to assess their knowledge is scarce. This study aimed to develop and validate an Antibiotic Knowledge Assessment Questionnaire (AKAQ). **Methods:** The AKAQ had three domains and 29 items, encompassing general antibiotic knowledge, antibiotic resistance, and antibiotic stewardship. Rasch analysis was used to assess psychometric properties, including validity parameters (item and person fit and structural validity), reliability (person and item reliability, Cronbach's Alpha value), item-person interaction, and item bias, using differential item functioning (DIF) based on tems. **Results:** This study included 500 undergraduate pharmacy students from 90 Indonesian universities. The validity of the questionnaire was demonstrated, except for one item. Person means infit and outfit for MNSQ were 1.02 and 0.95, whereas ZSTD were 0.11 and 0.08, respectively. Items means infit and outfit for MNSQ were 1.01 and 0.96, while ZSTD were 0.11 and -0.23. Item and person reliabilities were acceptable at 0.99 and 0.68. Cronbach's alpha reliability was acceptable at 0.71. Two items were biased by term. **Conclusion:** The AKAQ is a valid, reliable, and standard instrument for assessing the antibiotic knowledge levels of undergraduate pharmacy students.

Introduction

Antimicrobial resistance (AMR) is a global health issue (O'Neill, 2014), directly responsible for 1.27 million deaths in 2019, as estimated by a recent global analysis (Murray *et al.,* 2022). The impact of AMR is particularly pronounced in low-middle-income countries (O'Neill, 2014) compared to middle- or high-income countries due to weak laboratory capacity, inadequate governance of health systems, limited health information systems, and constrained resources (Iskandar *et al.,* 2021). Notably, Indonesia ranked 70th of 76 countries in the total amount of antibiotic consumption measured in DDD/1000 inhabitants per day, according to the pharmaceutical sales data between 2000 and 2015 (Klein *et al.,* 2018).

Recognising the critical role of proper education and training in addressing AMR, this work focuses on pharmacy students as future healthcare professionals. Some studies suggest that enhancing pharmacy students' knowledge of AMR and stewardship programmes can influence the broader population's behaviour towards responsible antibiotic use (Bond,

2005; Smith & Olin, 2010; Burns *et al.,* 2020). However, research data on antibiotic knowledge and antibiotic stewardship among pharmacy students is scarce; in developing countries, it is limited to Pakistan (Hayat *et al.,* 2021), Saudi Arabia (Kandasamy *et al.,* 2020), Uganda, Kenya, and Tanzania (Lubwama *et al.,* 2021), Sri Lanka (Sakeena *et al.,* 2018), and Malaysia (Rajiah *et al.,* 2015). Moreover, recent studies measured knowledge levels of antibiotics among the general population in Indonesia (Widayati *et al.,* 2012; Karuniawati *et al.,* 2021; Yunita *et al.,* 2022; Sinuraya *et al.,* 2023). Importantly, this research gap has not been addressed in the Indonesian context, where Rasch analysis was utilised. Unlike the commonly used factor analysis (Liu *et al.,* 2019; Karuniawati *et al.,* 2022; Tohan *et al.,* 2023), Rasch offers distinct advantages in evaluating structural validity (Mallah *et al.,* 2020). Factor analysis has drawbacks, such as the parametric basis of component analysis and the formation of "*difficulty factors*", which may falsely suggest multidimensionality with ordinal scales (Nunnally & Bernstein, 1994). In contrast, Rasch's analysis comprehensively assesses item function, differential item functioning, and local item dependencies (Bond *et al.,* 2020; Linacre, 2021). Rasch generates an ordered item collection, tests unidimensionality, ensures generalisability, considers the potential variability in how respondents perceive the distances between different response options, and identifies poorly functioning items through unexpected replies, providing valuable advantages (Bond *et al.,* 2020).

This study aimed to develop a valid and reliable instrument to measure Indonesian undergraduate pharmacy students' general knowledge of antibiotics, antibiotic resistance, and antibiotic stewardship.

Methods

Study design, participants, and setting

A web-based cross-sectional quantitative study was performed in Indonesia from February to May 2022 using the Antibiotic Knowledge Assessment Questionnaire (AKAQ), a self-administered instrument created on Google Forms. The questionnaire was distributed to Indonesian undergraduate bachelor of pharmacy students (an education programme before professional pharmacist education) from different terms and universities.

Ethics approval and informed consent

The study received ethical approval from the Health Research Ethics Committee of Universitas Harapan Bangsa before it was conducted (Reference No. B-LPPM-UHB/726/02/2022). The respondents were informed online about the nature of this study; they consented to participate by starting the AKAQ. The anonymity of the students was assured to protect their identification.

Sample size and recruitment

Comrey and Lee have categorised the quality of sample size for questionnaire validation based on the number of samples, i.e. the sample size of 50, 100, 200, 300, 500, and ≥1000 should be regarded as very poor, poor, fair, good, very good, and superb, respectively (Comrey & Lee, 2013). Therefore, the sample size was set to 500 participants to achieve an adequate level. This study applied a random sampling method to choose participants from Indonesian universities. Lecturers were approached from different universities to distribute the AKAQ to their students from different years of the bachelor programme. Data were transformed from the Google Form database into Statistical Package for the Social Sciences version 26.0 (IBM, 2019) to be exported into Winsteps version 5.2.1.0 software (Linacre, 2022). Rasch analysis was conducted, which is a psychometric analytic method that analysed participant responses to the AKAQ questionnaire to determine instrument validity and scale functioning. A Rasch model was used to analyse sum scores from these ordinal responses due to the dichotomous response structure to calculate interval-level estimates that represent person locations (i.e. person ability) and item locations (i.e. the difficulty of a specific question (item) to provide a correct or positive response) on a linear scale that represents the latent variable (logit scale) (Laliyo *et al*., 2022).

Instrument development

The four steps for developing the questionnaire consisted of framework development, item (question) generation, item screening, and pre-testing (Boateng *et al.,* 2018).

Framework development

Established questionnaires (Jamshed *et al.,* 2014; Inácio *et al.,* 2017; Lubwama *et al.,* 2021; Park *et al.,* 2021) and antimicrobial stewardship guidelines (World Health Organization, 2019; World Health Organization, 2021) were used for the framework development phase.

Item generation

Building upon the framework, the AKAQ was categorised into two parts. The first part is intended to collect information about participants' demographic

characteristics such as sex, age, and term. The second part assessed participants' knowledge of antibiotics and included three domains evaluating general antibiotic knowledge (Inácio *et al.,* 2017; Katzung & Vanderah, 2020), antibiotic resistance (Jamshed *et al.,* 2014; Lubwama *et al.,* 2021), and antibiotic stewardship (World Health Organization, 2019; Park *et al.,* 2021; World Health Organization, 2021). It comprised close-ended questions with the options of "*agree*," "*do not agree*," or "*do not know*." The scales were dichotomised, with true and false answers scored 1 and 0, respectively. Similar to wrong answers, the "*do not know*" option was graded 0.

Item screening

Item screening involved four experts (pharmacists with experience in teaching antibiotic-related topics to pharmacy students) who checked the relevance of the items. This process focused on establishing the content validity of the AKAQ items and entailed the exclusion of some questions that did not meet the predetermined criteria. The content validity of the AKAQ was assessed through the content validity index (CVI) approach. Excellent content validity should be composed of Item-CVI (I-CVI) to measure expert agreement on individual item's relevance, Scale-level CVI/Universal Agreement (S-CVI/UA) to gauge unanimous expert agreement on item relevance, and Scale-level CVI/Average (S-CVI/Ave), an average score indicating the degree of expert agreement on item relevance and appropriateness at the scale or questionnaire level, with threshold values of ≥0.78, ≥0.8, and ≥0.9, respectively (Shi *et al.,* 2012). The content of all the AKAQ items achieved the validity parameters. Finally, a questionnaire was constructed in Indonesian and comprised 29 items distributed over three domains, i.e. general knowledge (9 items), AMR (10 items), and antimicrobial stewardship (10 items) (Appendix A).

Pre-testing

The final stage of instrument development involved a pre-testing (face validity test) to examine the clarity of the items. Previous research suggested 30 people for pre-testing (Perneger *et al*., 2015). The AKAQ was distributed to 30 pharmacy students to confirm questionnaire readability and content before collecting data on a larger sample size. Questionnaire item correction and amendment were addressed according to their feedback. The latest version of the polished pre-testing question was utilised as the final questionnaire for validation (Appendix B).

Construct validity

The Rasch measurement analysis was used to investigate the AKAQ validity based on construct validity. This psychometric technique was developed to improve the precision of instrument (questionnaire) constructions, evaluate instrument quality, and investigate respondents' performances (Boone *et al*., 2014). The Rasch analysis accurately and precisely explained the difficulty level of an item (i.e. question), detected the suitability and interaction of items and persons (item-person maps), identified outliers (person misfit), and detected item bias (e.g., differential item functioning (DIF)) to ensure that all items consistently measure the same concept across different term (Boone, 2016; Sumintono & Widhiarso, 2014). Rasch measurement was based on the Joint Maximum Likelihood Estimation equations whereby the raw data were converted to interval data (logits)(Linacre, 1998; Bon, Fox & Lacey, 2020). Psychometric parameters of the AKAQ, which were assessed consisting of validity parameters (item and person fit, structural validity); reliability (person and item reliability, Cronbach's Alpha value; person and item separation); item-person interaction; and item bias using DIF based on term (see Table I).

Table I: Rasch measurement properties and assessment criteria

Rasch measurement	Acceptable range	Definition
Person and item fit analysis	The person and item fit were measured using infit and outfit mean-square (MNSQ) and z-standard (ZSTD). The acceptable range of infit and outfit MNSQ are 0.5–1.5 (Sumintono & Widhiarso, 2015; Bond *et al.,* 2020). The value of 1.6 is accepted if an item has a positive point measure correlation (PTMA) (Sumintono & Widhiarso, 2015; Bond *et al.,* 2020) Meanwhile, the acceptable range for infit and outfit of ZSTD is −2 to +2, even though this threshold can be ignored if the sample size is more than 200 (Azizan *et al.,* 2020)	Person fit analysis was used to determine the validity of the person-response relationship. It can help to identify participants with atypical response patterns (for example by selecting the same answer for all the items). Item fit analysis was conducted to see whether the items in the AKAQ instruments can measure the knowledge about antibiotics in pharmacy undergraduate students. The item should be improved or deleted if a particular item is a misfit. Item fit analysis was displayed on a bubble chart to show measures and fit values graphically.

Rasch measurement	Acceptable range	Definition
Structural validity (unidimensionality)	Raw variances of >30% (Linacre, 1998; Chou & Wang, 2020) Eigen values of <3 (Linacre, 2021)	Structural validity measurement aimed to ascertain whether all items collectively measure the same domain of knowledge trait. The parameters of unidimensionality were assessed to confirm the structural validity of the AKAQ. Unidimensionality was evaluated by raw variances explained by items and unexplained variances in first contrast or Eigen values.
Reliability	Person and item reliability of >0.67 (Fisher, 2007) Cronbach's alpha value of >0.6 (Taber, 2018)	Reliability is measured to indicate the reproducibility of the measure (Linacre, 2021), (Bond & Fox, 2013).
Separation coefficients for individual items and persons	Item separation value is expected as >3 (Linacre, 2021). Person separation values are 1.50 (acceptable), 2.00 (good), and 3.00 (excellent)(Duncan *et al.,* 2003; Canto-Cerdan *et al.,* 2021)	The separation coefficient was measured to explore how well the different items distinguish the participants' ability and how well the individual participants distinguish the items' difficulty levels. The higher the separation values, the better the separation.
Item-person interaction	Item-person interaction is displayed in the Wright map (see Fig. 2 in results) using the same linear scale (logit scale). It was assessed from a distance between the mean (M) value of items' difficulty and participants' ability. The closer the two values, the better, with a difference of 0 between the two values denoting a perfect match between the items' difficulty and participants' ability. A difference of 1> logit indicates a non-matching difficulty level between the question/item and the participants' ability (Cantó-Cerdán *et al.,* 2021)	Wright Map (Item-Person Correlation) is intended to explore how well the distribution of test items' difficulty concerning participants' knowledge levels.
Differential Item Functioning (DIF)	Negligible (|DIF | 0≥0.43 logits); Slight to Moderate (|DIF | ≥0.43 logits) and prob (|DIF| = 0 logits) ≤0.05 (2-sided); Moderate to Large (|DIF | ≥0.64 logits) and prob(|DIF| ≤0.43 logits) ≤0.05 (2-sided) (Zwick *et al.,* 1999)	DIF is conducted to check item bias based on the term in which we assume that students from different terms will have different scores on the AKAQ (Linacre, 2021). Term classification is divided into two groups, i.e. undergraduate pharmacy students in the first to fifth terms and sixth to twelfth terms, but undergraduate pharmacy education in Indonesia should be noted to have a standard study period of 4 years or 8 terms, while students above 8 terms are students who are late in completing their studies.

Statistical analysis

This study used Winsteps version 5.2.1.0 software (Linacre, 2022) and Statistical Package for the Social Sciences (SPSS) version 26 (IBM, 2019) for statistical analysis. Winsteps was used to perform Rasch analysis to check the validity and reliability of the AKAQ and to run a DIF analysis. The SPSS version 26 (IBM, 2019) was used to run the descriptive statistics of participants' characteristics.

Results

Data collection and screening

This study enrolled 500 participants from 90 Indonesian universities (Table II). Of the total sample, 85% were females, 59% were 20-23 years old, and 30.4% were in the fourth term. The majority (69.0%) were from universities in the western region of Indonesia, where most universities are located.

Table II: Demographics of participants (n=500)

Baseline characteristics	Frequency	%
Sex		
Female	425	85%
Male	75	15%
Age		
<20 years old	117	35.4%
20-23 years old	294	58.8%
>23 years old	29	5.8%
Term		
1st – 5th Term	282	56.4%
6th – 12th Term	218	43.6%
University participants		
West Region (69 Univ.)	345	69.0%
Central Region (20 Univ.)	126	25.2%
East Region (1 Univ.)	29	5.8%

AKAQ validity and reliability

The Person and Item Fit Parameters are summarised in Table III. Overall, the means of infit (weight) and outfit (unweight) mean square (MNSQ) for person fit measurements were acceptable, with values of 0.93 and 1.00, respectively. The means of infit and outfit z-standard (ZSTD) were acceptable, with values of 0.03 and 0.06, respectively. However, approximately 11% of participants (n = 56) were misfits (Appendix C) because their infit and outfit MNSQ were outside the acceptable range (lower threshold: 0.5, and upper threshold: 1.6 as long as the value of PTMA is positive) (Sumintono & Widhiarso, 2015; Bond *et al.,* 2020). Thus, the response pattern of those students could not be predicted well by the Rasch model. The misfit persons were excluded; hence, the MNSQ and ZSTD person values after exclusion were acceptable, with values of 0.95 and 1.02 and 0.11 and 0.08, respectively. Some persons were misfits based on the ZSTD threshold (n = 20). However, the number of samples is 444 (>200); therefore, this ZSTD threshold can be ignored (Azizan *et al.,* 2020).

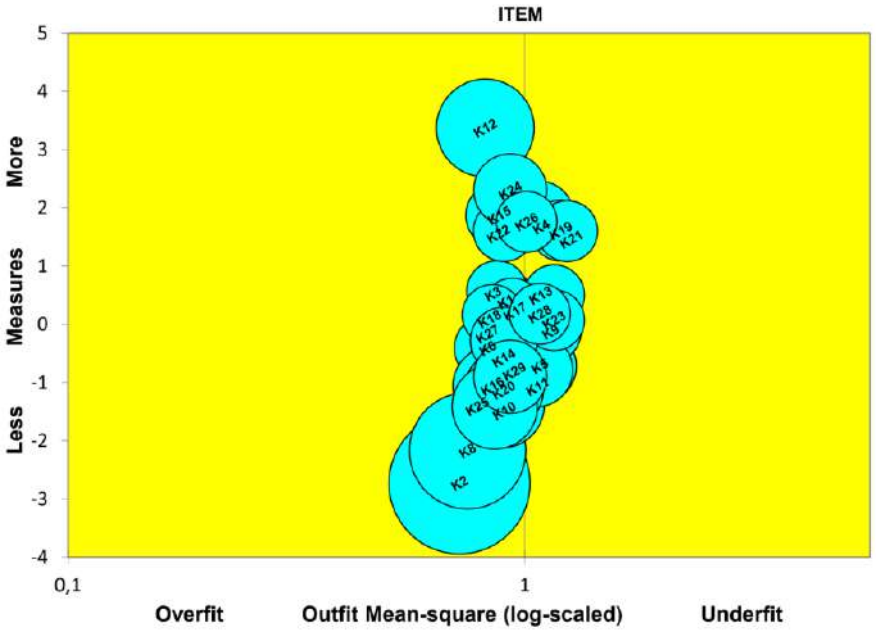
Table III: Summary of Rasch parameters for AKAQ

	Persons	Person (After deletion)	Item (question)	Item (After deletion K7)
N	500	444	29	28
Mean measure	0.78	0.75	0.00	0.16
SD	0.80	0.69	1.61	1.41
SE	0.04	0.04	0.31	0.27
Mean:				
Infit MNSQ	1.00 (Range: 0.43-1.69)	1.02 (Range: 0.61-1.69)	1.00 (Range:0.82-1.16)	1.01 (Range:0.89-1.16)
Infit ZSTD	0.03 (Range: -2,85-2.5)	0.11 (Range: -1.90-2.44)	0.09 (Range:-2.72-4.46)	0.11 (Range:-2.72-4.46)
Outfit MNSQ	0.93 (Range: 0.14- 2.73)	0.95 (Range: 0.50-1.58)	0.93 (Range: 0.17-1.24)	0.96 (Range:0.73-1.24)
Outfit ZSTD	0.06 (Range:-1.33-2.80)	0.08 (Range:-1.13-1.27)	-0.30 (Range:-2.55-2.85)	-0.23 (Range:-2.55-2.85)
Reliability (Rasch)	0.73	0.68	0.99	0.99
Reliability (Cronbach's Alpha)	0.71			
Separation coefficient	1.65	1.44	10.83	11.40
Unidimensionality				
Raw variance by measure	34.9%			
Unexplained variance in 1st contrast	2.84%			

*SD= Standard Deviation, SE= Standard error, MNSQ= mean-square, ZSTD= z-standard, K7= Knowledge Question no.7

The means of infit and outfit were 1.00 and 0.93 for MNSQ and -0.30 and 0.09 for ZSTD, respectively, for the item fit. However, one misfit item was identified based on the MNSQ outfit value (Appendix D), i.e. item K7 (MNSQ: 0.17; ZSTD: −2.18). Thus, this item was removed (Appendix E). The deletion of item K7 was able

to increase MNSQ and ZSTD outfits (Table III). Furthermore, ten misfit items were found (Appendix D) according to the range of ZSTD infit and outfit value (−2–2), but this threshold can be ignored because the sample size is >200 (Azizan *et al.,* 2020). The distribution of item fit orders for the 28 valid items is shown in Figure 1, while the initial item fit order involving item K7 is shown in Appendix E.



The Y axis is the Joint Maximum Likelihood Estimation (item) Measure; the X axis is the Item Fit Mean Square (Linacre, 2021); Overfit (x > 1.50); Outfit (x = 0.50–1.50). Each bubble represents an item whose size is proportional to the standard error of item difficulty calibration. Well-fitting items are close to the central vertical line. Items should preferably be the closest possible to a modelled value of 1 for infit and outfit MNSQ, regardless of plotting the interplay of fit and items and fit and persons (Bond *et al.,* 2020).

Figure 1: Bubble chart of item fit order

Construct validity (unidimensionality)

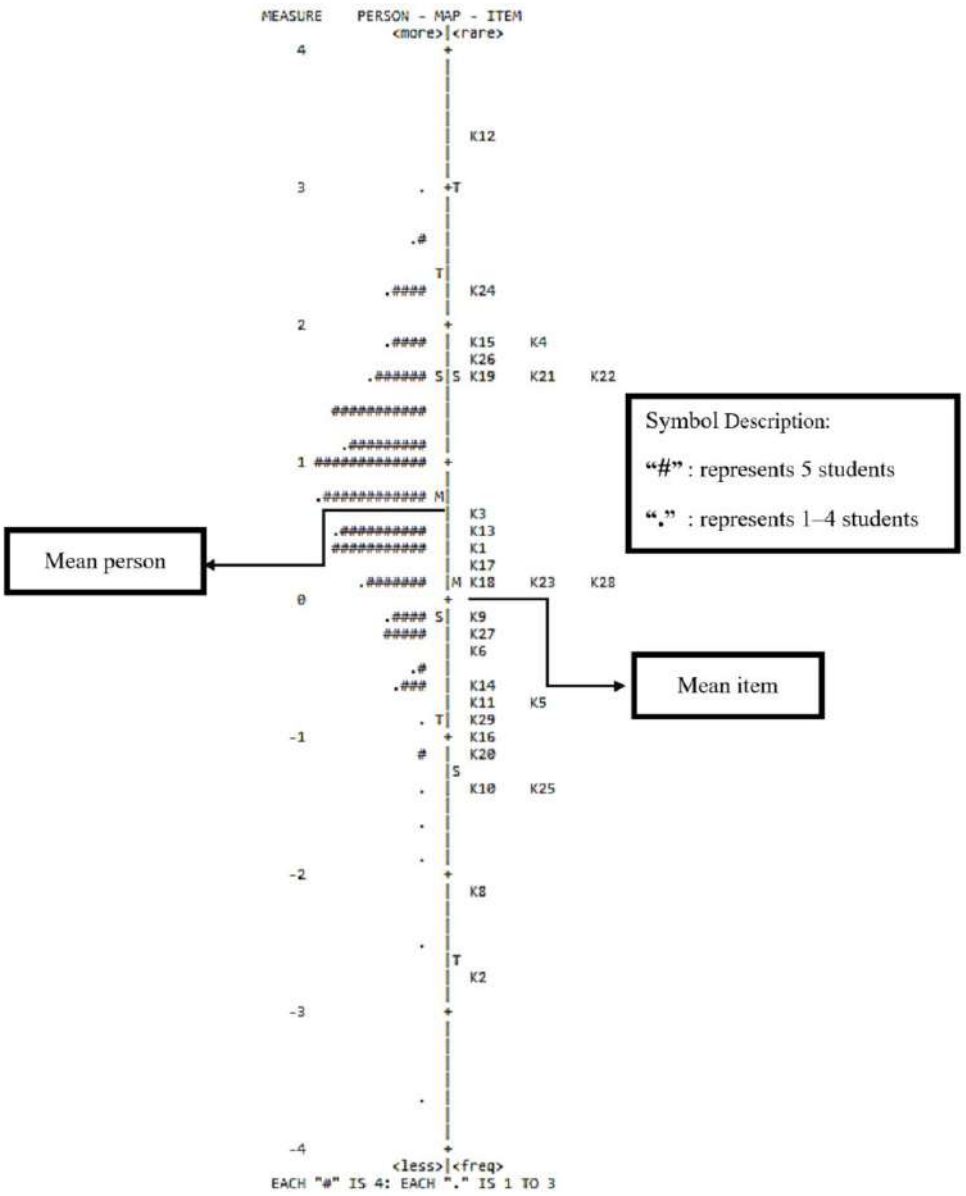
The structural validity of the AKAQ was further examined using unidimensionality. The results reached an acceptable threshold at >30% (Linacre, 1998; Chou & Wang, 2010) (33.4%), indicating that the instrument achieved the unidimensionality criteria. Moreover, the unexplained variance for the first contrasting values was <3% (2.71%). The unexplained variance confirms no random noise in the instrument used in this study.

Reliability

The Rasch parameter generated acceptable criteria for person and item reliabilities, i.e. 0.7 and 0.9, respectively. Additionally, Cronbach's alpha was above the acceptable threshold, i.e. 0.6 (Taber, 2018) (Table III). Overall, the AKAQ exhibited acceptable criteria for the Rasch reliability parameter (Fisher, 2007; Taber, 2018). Moreover, the person and item separations were acceptable, i.e. 1.44 and 20.08, respectively. These values supported the idea of the AKAQ reliability (Wright & Master, 1982; Boone, 2016).

Item-person interaction

The item-person Wright map (Figure 2) was used to check whether the items in the AKAQ were neither too challenging nor too easy for the participants. In this study, the participants' indicators were located higher than the items' indicators, reflecting that pharmacy students had a higher ability than the difficulty level of the test items (Linacre, 2021). However, the difference between the mean person measure and the mean items measure was <1 logit (0.51 logits), which indicates that the difficulty level of the question/item remained suitable with the participants' ability (Linacre, 1998; Linacre, 2021). Hence, item K2 (Bacterial infections can be treated with antibiotics) was identified as the easiest item and item 12 (Beta-lactamases are enzymes produced by bacteria that break open the beta-lactam ring) was the hardest item (Boone, 2016).



The right-hand side shows the 28 items of the questionnaire from the easiest (K2, bottom indicator) to the most difficult one (K12, top indicator); the left-hand side locates the person's ability measured along with the items. The higher the symbol, the better the test results. M in the right- and left-hand sides indicate the mean item difficulty and the mean person ability, respectively (Canto Cerdan *et al*., 2021).

Figure 2: Wright map (Item-Person Correlation)

Moreover, the Wright map shows that students have >50% chance (p = 0.5) of correctly answering an item when their indicator is above the item's indicator. The 50% chance (p = 0.5) occurs when the indicators align, indicating comparable difficulty levels between the item and students' ability. Conversely, students have <50% (p < 0.5) chance to correctly answer the item if the person's indicator is located the item's indicator.

Differential Item Functioning (DIF) analysis

DIF analysis by term (Figure 3) indicated that items K6 (DIF:0.79; Prob:0.0045) and K19 (DIF: −0.67; Prob: 0.0198) fell into the moderate to large DIF category (Zwick *et al.,* 1999) (Appendix F). Items K6 and K19 were found to be easier for students in the first to the fifth terms compared to those in the sixth to the twelfth terms. However, these items were not removed because they are relevant for assessing antibiotic-related knowledge, supported by the content and construct validity results. Moreover, dropping these items might lower the reliability and validity of the AKAQ (Zwick *et al.,* 1999; Gothwal *et al.,* 2009).

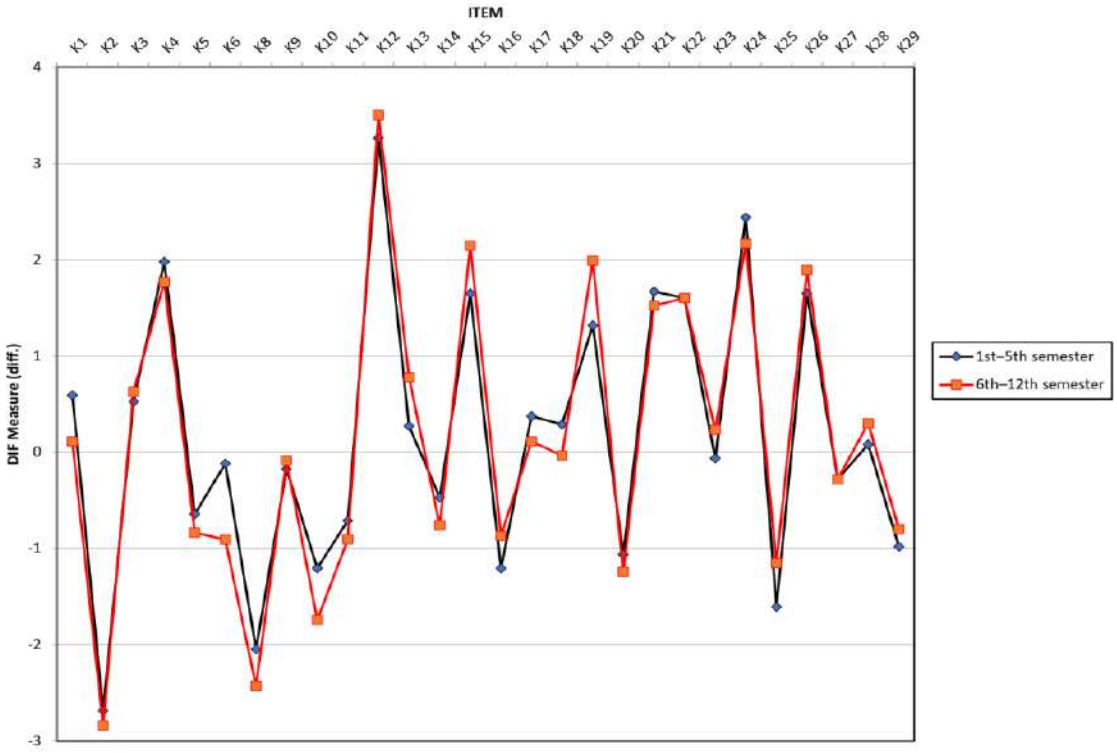


Figure 3: DIF based on the term

Discussion

This study is the first to develop AKAQ using the Rasch measurement model as a psychometric analysis. Rasch analysis is different from item response theory, which is a scale characterised by a positive correlation between the ability of respondents and the probability of respondents favouring more challenging items (Streiner & Norman, 2008). Rasch measurement can solve several problems in assessing misconceptions that cannot be resolved based on classical test theory, such as detecting the difficulty level of an item accurately and precisely, determining the misfit of items and persons, and identifying DIF items (Boone *et al.,* 2014; Adams *et al.,* 2020).

Linacre (Linacre, 1998; Linacre, 2021) established ideal ranges for infit and outfit MNSQ and ZSTD scores to minimise the inclusion of misfitting items (questions) and persons. AKAQ was analysed using Rasch analysis, and the results show that these questionnaires have a good model fit for the 28 items and 447 persons in the final tool based on MNSQ and ZSTD scores. However, this study revealed 56 persons with misfit MNSQ values (Appendix B) but positive point measure correlations (PTMEA Corr). Examination of the PTMEA Corr detects polarity items intended to examine whether or not the items in AKAQ measure the same dimension. A zero or negative value indicates a conflict with the variable or construct for the item response or respondent (Linacre, 2021). Items with positive PTMEA (+) values show that the item measuring the construct can distinguish between the ability of the respondents (Bond *et al.,* 2020). However, the persons with misfit values were excluded because those do not bring efficiency to building measurements of the questionnaire (Linacre, 1998; Wright & Stone, 1998).

Identifying and excluding misfitting items and persons in the AKAQ were crucial steps in refining the questionnaire. Linacre (Linacre, 1998; Linacre, 2021) established ideal ranges for infit and outfit MNSQ and ZSTD scores to minimise the inclusion of misfitting items (questions) and persons.

The decision to exclude specific items was based on rigorous analysis, considering both statistical indicators and practical implications. One item misfit (K7) was found based on outfit MNSQ value. K7 item (amoxicillin is an antibiotic) had the lowest difficulty level (Appendix F), yielding a 99.0% percentage of correct answers. Therefore, it was excluded due to its consistently high correct response rates, indicating a lack of variability among respondents. Retaining such items would compromise the measurement of antibiotic knowledge, as they fail to effectively differentiate between respondents with varying knowledge levels. The rationale underlying the removal

of specific items was guided by the principles of measurement efficiency and construct validity. Items with misfitting values were considered inefficient in enhancing AKAQ's accuracy. The goal was to ensure that the remaining items collectively formed a questionnaire with optimal fit validity and internal consistency, meeting psychometric standards. After exclusion, the AKAQ demonstrated improved utility, providing a more robust and efficient assessment of antibiotic knowledge. Reliability test results indicated that the questionnaire had acceptable to high internal consistency, as set by the National Quality Forum's Measure Evaluation Criteria (National Quality Forum, 2021).

The AKAQ is expected to achieve the unidimensionality criteria. The unidimensionality result confirms that all items in AKAQ measure one-dimensional antibiotic knowledge, including general knowledge of antibiotics, AMR and AMS. All unidimensionality parameters confirming the construct validity of the AKAQ achieved an acceptable threshold (Linacre, 1998; Brentani & Silvia, 2007; Linacre, 2021).

The item-person analysis indicates that all items could measure student abilities in antibiotic-related knowledge, spanning from low to high proficiency. The construction of the items, from the easiest at the bottom to the hardest at the top of the Wright map, enables a proper evaluation to capture the range of student abilities (Linacre, 1998; Linacre, 2021). The item about the ability of beta-lactamase enzyme to destroy the beta-lactam ring was the most challenging item to answer by pharmacy students, and similar findings have been reported in previous studies from the United Kingdom (Inácio *et al.,* 2017) and Pakistan (Hayat *et al.,* 2021). The question related to the mechanism of antibiotic resistance was difficult for pharmacy students to adequately answer, probably because of the inadequate education in the pharmacy curriculum, especially for students in the first part of the curriculum (first to fifth terms) than in the second part of the curriculum (sixth to twelfth terms). The least complicated item in the AKAQ (after excluding K7) was the statement about whether bacterial infections could be cured with antibiotics (K2). This finding is supported by previous studies from the United Kingdom (Inácio *et al.,* 2017) and Sri Lanka (Zawahir *et al.,* 2017), where the item related to the efficacy of antibiotics in treating bacterial infection was also correctly answered by more than 95% of the sample.

Furthermore, the DIF analysis revealed that only two of the 28 items were biased based on terms (Appendix F). DIF items were found only in K6 and K19 because these items are easier for students in the sixth to twelfth terms compared to those in the first to fifth terms. No other DIF items could explain the difference between pre-final and final-year students. The results from China (Huang *et al.,* 2013) support these findings that pre-final year students had more knowledge than students in early-year terms, likely due to their updated knowledge of pharmacology (including antibiotic courses), which they have completed in the past year. However, these items were still retained to analyse the psychometric properties of the developed test because all questionnaire items were valid and reliable.

The application of Rasch analysis in developing the AKAQ holds multifaceted significance for antibiotic knowledge assessment. Rasch analysis elevates the precision of knowledge measurement by identifying and excluding misfitting items and respondents through meticulous examination of MNSQ and ZSTD values. The fit values of MNSQ and ZSTD verify that the questionnaire achieves the validity criteria, indicating that AKAQ items measure antibiotic knowledge as a target construct appropriately based on Rasch parameters. Therefore, confirming MNSQ and ZSTD values means ensuring the effectiveness and precision of the AKAQ questionnaire.

The rigorous validation process, guided by Linacre's criteria, yields a questionnaire with strong fit validity and high internal consistency, meeting the Measure Evaluation Criteria of the National Quality Forum (NQF), establishing the AKAQ as a psychometrically robust tool for assessing antibiotic knowledge. Confirmation of unidimensionality criteria validates that all items measure a single dimension, i.e. antibiotic knowledge, strengthening questionnaire construct validity.

The present study demonstrates AKAQ's efficacy in measuring students' abilities across a spectrum of antibiotic-related knowledge, providing a comprehensive evaluation from fundamental concepts to more specific knowledge items. Beyond methodological contributions, the Rasch-validated AKAQ holds practical implications globally, allowing educators to customise pharmacy school curricula, ensuring the instrument is relevant and impactful in enhancing antibiotic knowledge education.

Limitations

This study has some limitations. First, pharmacy education in Indonesia is diverse, with no standardised curricula, inducing potential bias that may influence the external validity of results. Moreover, the AKAQ included items covering basic antibiotic knowledge, aligning with the intention to assess a broad spectrum of knowledge applicable to students in the first part of their curriculum. Therefore, while this study provides valuable insights into antibiotic knowledge among

Indonesian undergraduate pharmacy students, caution should be exercised when extrapolating the findings to different educational contexts. Data were self-reported by participants who were voluntarily recruited via WhatsApp, introducing the possibility of selection bias. Additionally, the dominance of students from some universities in the sample may impact the study's external validity. Social media recruitment channels such as WhatsApp might attract specific demographics, potentially influencing the level of antibiotic knowledge reported. Further studies are recommended to validate the questionnaire among global student populations and different educational levels. Additionally, the study only performed a DIF analysis to understand the difference based on terms; thus, further DIF analysis would be warranted to compare gender differences.

Conclusion

The AKAQ was successfully developed and validated to assess knowledge about antibiotics in undergraduate pharmacy students in Indonesia. The AKAQ achieved adequate fit validity and reliability criteria using the Rasch analysis, affirming its psychometric robustness. Rasch analysis provides a valuable tool for evaluating AKAQ's psychometric aspect and adds to existing methods. The instrument shows promise in facilitating targeted educational interventions and advancing antibiotic stewardship initiatives. Further research is required to determine the instrument's applicability across diverse pharmacy students worldwide and educational levels.

List of abbreviations

AKAQ: antibiotic knowledge assessment questionnaire
MNSQ: mean-square
ZSTD: z-standard
DIF: differential item functioning
AMR: antimicrobial resistance
CVI: content validity index
UA: universal agreement
AMS: antimicrobial stewardship
JMLE: joint maximum likelihood estimation
IRT: item response theory
CTT: classical test theory
PTMEA Corr: positive point measure correlations
K: knowledge item

Conflict of interest

The authors declare no conflict of interest.

Authors' Contributions

IYK, and MAB; methodology, formal analysis, software: IYK, MAB, and SS; ethics and data collection: DAN and RP, investigation: IYK, MAB, MM and RB; data curation and validation: MM and RB; writing—original draft preparation: IYK, MAB, MM and RB; writing—review and editing: MM, RB, DC; and funding acquisition: DC. All authors have read and approved the final version of the manuscript.

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Appendix A: Content Validity Index (CVI) of the 29-items draft AKAQ from 4 experts

Variable construct	Panel 1		Panel 2		Panel 3		Panel 4		Expert in agreements	I-CVI Score	S-CVI score
	n	Code	n	Code	n	Code	n	Code			
K1	4	1	4	1	4	1	4	1	4	1.00	1
K2	4	1	4	1	4	1	3	1	4	1.00	1
K3	4	1	4	1	4	1	3	1	4	1.00	1
K4	4	1	4	1	4	1	4	1	4	1.00	1
K5	4	1	3	1	4	1	4	1	4	1.00	1
K6	4	1	4	1	4	1	4	1	4	1.00	1
K7	4	1	4	1	4	1	4	1	4	1.00	1
K8	4	1	4	1	4	1	4	1	4	1.00	1
K9	3	1	4	1	4	1	3	1	4	1.00	1
K10	4	1	4	1	4	1	3	1	4	1.00	1
K11	4	1	4	1	4	1	4	1	4	1.00	1
K12	3	1	3	1	4	1	4	1	4	1.00	1
K13	4	1	4	1	4	1	3	1	4	1.00	1
K14	4	1	4	1	4	1	3	1	4	1.00	1
K15	4	1	4	1	4	1	4	1	4	1.00	1
K16	4	1	4	1	4	1	4	1	4	1.00	1
K17	4	1	4	1	4	1	3	1	4	1.00	1
K18	4	1	4	1	4	1	4	1	4	1.00	1
K19	4	1	4	1	4	1	4	1	4	1.00	1
K20	4	1	3	1	4	1	4	1	4	1.00	1
K21	4	1	4	1	4	1	4	1	4	1.00	1
K22	4	1	4	1	4	1	4	1	4	1.00	1
K23	4	1	4	1	4	1	4	1	4	1.00	1
K24	4	1	4	1	4	1	4	1	4	1.00	1
K25	4	1	4	1	4	1	4	1	4	1.00	1
K26	4	1	4	1	4	1	4	1	4	1.00	1
K27	3	1	4	1	4	1	4	1	4	1.00	1
K28	4	1	4	1	4	1	4	1	4	1.00	1
K29	4	1	4	1	4	1	4	1	4	1.00	1
Mean			1.00		1.00		1.00	1.00	Summary	30.00	30.00
Average proportion of items judged as relevance (4 experts): 1.00									Average	1.00	1.00
									Conclusion	Acceptable	Acceptable

*I-CVI, item level content validity index; S-CVI, scale level content validity index

Appendix B: All items of AKAQ and percentage of answers by category response

Item	Questions	Correct answer
GENERAL KNOWLEDGE OF ANTIBIOTICS		
K1	Antibiotics are useful for viral infections	41.2%
K2	Bacterial infections can be treated with antibiotics	95.6%
K3	Antibiotics can be used to cure colds	45.0%
K4	Pain and inflammation can be treated with antibiotics	71.8%
K5	Antibiotics can cause allergic reactions	78.8%
K6	Aspirin is an antibiotic	26.0%
K7	Amoxicillin is an antibiotics	99.0%
K8	Antibiotics must be obtained with a doctor's prescription	93.0%
K9	All antibiotics must be taken before eating	30.8%
ANTIBIOTICS RESISTANCE		
K10	Resistance occurs when bacteria lose its sensitivity to antibiotics	87.0%
K11	Bacteria can alter membrane permeability and cause resistance	79.6%
K12	Beta-lactamases are enzymes produced by bacteria that break open the beta-lactam ring	9.2%
K13	Prescribing broad-spectrum antibiotics increases antibiotics resistance	56.6%
K14	Independent use of antibiotics can increase antibiotic resistance	76.8%
K15	The use of narrow-spectrum antibiotics is more at risk of causing resistance than broad-spectrum antibiotics	71.6%
K16	Sensitivity tests and bacterial culture tests are able to minimize resistance and determine the appropriate antibiotic	83.4%
K17	Antibiotics can be used independently if you have already used the same antibiotic	38.6%
K18	Antibiotics can be used by other people with the same symptoms	36.4%
K19	Bacteria that are resistant to antibiotics can be passed from one person to another	33.2%
ANTIBIOTIC STEWARDSHIP		
K20	Antibiotic stewardships an effort to optimize the use of antibiotics in patients	84.2%
K21	Antibiotics are overused Nationally and Internationally in healthcare	33.4%
K22	The sale of narrow-spectrum antibiotics without a prescription is a form of antibiotic stewardship	66.6%
K23	Rapid diagnostic tests enable more accurate diagnosis, specific antibiotic treatment and decrease antibiotic resistance	65.4%
K24	The use of combinations of antibiotics with the same spectrum reduces resistance	78.8%
K25	The study of the consumption of antibiotics and the manufacture of formularies is a preventive measure against the occurrence of antibiotic resistance	87.2%
K26	Stopping the use of antibiotics for livestock does not prevent antibiotic resistance	69.6%
K27	Antibiotic stewardship will reduce antibiotic resistance	71.8%
K28	Antibiotic stewardship improve cost-effectiveness in the health care sector	63.2%
K29	Antibiotic stewardship improve collaboration between health care providers	81.4%

*K, knowledge item

Appendix C: Person fit measurement

No	COUNT	SCORE	INFIT MNSQ	INFIT ZSTD	OUTFIT MNSQ	OUTFIT ZSTD	PTMA	RMSR
1	29	12	1,1624	0,8712	2,7278	2,8027	0,3753	0,445
2	29	17	1,4523	1,9415	1,8227	1,4418	0,2737	0,4946
3	29	18	1,0393	0,251	1,8149	1,3418	0,4547	0,4128
4	29	24	1,1135	0,4511	1,8034	1,0518	0,3282	0,3481
5	29	16	1,2479	1,2012	1,7456	1,4217	0,3689	0,4629
6	29	14	1,543	2,4915	1,7004	1,4517	0,2481	0,5182
7	29	12	1,2671	1,3513	1,692	1,4317	0,3584	0,4646
8	29	25	1,1418	0,5011	1,6544	0,8917	0,2757	0,3268
9	29	17	1,4722	2,0115	1,6504	1,2117	0,2835	0,498
10	29	22	1,6393	2,1016	1,65	0,9717	0,1708	0,4673
11	29	13	1,3457	1,7013	1,6398	1,3616	0,3281	0,4824
12	29	22	1,5429	1,8315	1,6281	0,9516	0,1995	0,4533
13	29	22	1,5538	1,8616	1,626	0,9516	0,2023	0,455
14	29	15	1,0358	0,251	1,6103	1,2716	0,4762	0,424
15	29	16	1,1341	0,7011	1,6077	1,2216	0,4265	0,4412
16	29	14	1,5252	2,4215	1,6063	1,3016	0,2709	0,5152
17	29	14	1,4106	1,9614	1,5843	1,2616	0,3108	0,4954
18	29	13	1,4157	2,0014	1,5837	1,2716	0,3153	0,4948
19	29	16	1,1914	0,9512	1,5827	1,1816	0,4116	0,4523
20	29	19	1,2266	0,9912	1,5798	0,9916	0,3578	0,4404
21	29	20	1,0424	0,251	1,5744	0,9316	0,452	0,397
22	29	11	1,4055	1,8914	1,5722	1,1916	0,3123	0,4831
23	29	15	1,2182	1,1012	1,5689	1,2116	0,395	0,4598
24	29	16	1,1371	0,7111	1,563	1,1516	0,4321	0,4418
25	29	24	1,5351	1,5715	1,5527	0,8416	0,1725	0,4087
26	29	19	1,4203	1,6814	1,5526	0,9616	0,297	0,474
27	29	20	1,2624	1,0813	1,5449	0,9015	0,341	0,4368
28	29	17	0,969	-0,079	1,542	1,0615	0,5029	0,404
29	29	20	1,6898	2,4417	1,5395	0,8915	0,1915	0,5054
30	29	24	1,1369	0,5211	1,5253	0,8215	0,3235	0,3517
31	29	20	0,9288	-0,2191	1,5247	0,8815	0,4948	0,3747
32	29	20	1,3748	1,4714	1,5121	0,8615	0,3066	0,4559
33	29	15	1,5221	2,3615	1,5058	1,1115	0,2764	0,514
34	29	20	1,3813	1,4914	1,4905	0,8415	0,3095	0,4569
35	29	15	1,1392	0,7411	1,4839	1,0715	0,4332	0,4447
36	29	18	1,3968	1,6714	1,4797	0,9215	0,3146	0,4785
37	29	18	1,1566	0,7512	1,4763	0,9215	0,417	0,4354
38	29	19	1,4258	1,7014	1,4664	0,8615	0,3025	0,4749
39	29	15	1,1638	0,8612	1,4663	1,0415	0,4279	0,4494
40	29	17	0,8645	-0,5991	1,4597	0,9415	0,5498	0,3816
41	29	24	1,3884	1,2014	1,4453	0,7414	0,2398	0,3887
42	29	17	1,4689	2,0015	1,4428	0,9214	0,2999	0,4974
43	29	17	1,0952	0,5111	1,4334	0,9014	0,4422	0,4295
44	29	18	1,2514	1,1213	1,4311	0,8614	0,3803	0,4529
45	29	4	1,359	0,9114	1,4256	0,7114	0,2872	0,3405
46	29	22	1,1725	0,7012	1,4188	0,7414	0,3596	0,3952
47	29	9	1,3643	1,5414	1,4164	0,8514	0,3405	0,4557
48	29	19	1,2876	1,2113	1,4141	0,7914	0,3551	0,4513
49	29	12	1,2021	1,0512	1,4123	0,9614	0,4053	0,4525
50	29	18	1,1987	0,9212	1,4098	0,8314	0,4014	0,4433
51	29	15	1,5007	2,2715	1,4085	0,9414	0,2986	0,5103
52	29	17	1,3907	1,7114	1,3994	0,8514	0,3325	0,484
53	29	22	1,377	1,3514	1,3988	0,7214	0,2831	0,4283
54	29	19	0,9688	-0,059	1,3929	0,7614	0,4954	0,3914
55	29	22	1,1292	0,5511	1,3863	0,7114	0,3886	0,3878
56	29	19	1,4001	1,6114	1,3857	0,7514	0,3182	0,4706
57	29	13	1,2687	1,3713	1,3797	0,9214	0,3901	0,4684
58	29	17	1,072	0,4011	1,3796	0,8214	0,4643	0,4249
59	29	13	1,2692	1,3713	1,371	0,9014	0,3864	0,4685
60	29	22	1,2977	1,1113	1,3697	0,6914	0,3162	0,4158
61	29	17	1,4635	1,9815	1,3684	0,8014	0,3107	0,4965

No	COUNT	SCORE	INFIT MNSQ	INFIT ZSTD	OUTFIT MNSQ	OUTFIT ZSTD	PTMA	RMSR
62	29	8	0,91	-0,2991	1,3679	0,7414	0,515	0,3602
63	29	17	1,4694	2,0015	1,3664	0,8014	0,3094	0,4975
64	29	21	1,2612	1,0413	1,3636	0,6814	0,3566	0,4245
65	29	15	1,2605	1,2913	1,3631	0,8614	0,3918	0,4677
66	29	18	1,3788	1,6014	1,3555	0,7514	0,335	0,4754
67	29	20	1,2476	1,0312	1,3533	0,6914	0,365	0,4343
68	29	19	1,2335	1,0112	1,351	0,7114	0,3831	0,4417
69	29	18	1,3851	1,6214	1,3494	0,7413	0,335	0,4765
70	29	16	1,4068	1,8414	1,3464	0,8013	0,3364	0,4914
71	29	18	1,438	1,8114	1,3239	0,7013	0,32	0,4855
72	29	18	1,438	1,8114	1,3239	0,7013	0,32	0,4855
73	29	17	1,076	0,4211	1,3207	0,7313	0,4647	0,4257
74	29	24	1,1517	0,5612	1,3144	0,6213	0,3308	0,354
75	29	11	1,1285	0,6911	1,313	0,7613	0,4422	0,4329
76	29	19	1,1367	0,6411	1,3126	0,6613	0,4192	0,424
77	29	15	1,0503	0,3211	1,3121	0,7713	0,4886	0,4269
78	29	19	1,0877	0,4411	1,3061	0,6513	0,4428	0,4148
79	29	19	1,3417	1,4113	1,3057	0,6513	0,3533	0,4607
80	29	19	1,3197	1,3313	1,2997	0,6413	0,3561	0,4569
81	29	11	1,1611	0,8412	1,2932	0,7313	0,4316	0,4391
82	29	21	1,3533	1,3414	1,2915	0,6013	0,3231	0,4397
83	29	18	1,3328	1,4313	1,2883	0,6513	0,3631	0,4674
84	29	21	1,3412	1,3013	1,2878	0,6013	0,3271	0,4378
85	29	19	1,1957	0,8712	1,284	0,6213	0,4061	0,4349
86	29	23	0,8479	-0,4592	1,2821	0,5913	0,487	0,3216
87	29	24	1,0884	0,3811	1,2812	0,5913	0,3548	0,3442
88	29	24	1,2333	0,7912	1,279	0,5813	0,31	0,3663
89	29	19	1,2366	1,0312	1,2676	0,6013	0,392	0,4422
90	29	21	1,1357	0,6011	1,2675	0,5813	0,4097	0,4028
91	29	19	1,2998	1,2613	1,2617	0,5913	0,3685	0,4534
92	29	11	1,3178	1,5313	1,2601	0,6713	0,3788	0,4678
93	29	21	1,2091	0,8612	1,2591	0,5713	0,3766	0,4156
94	29	15	0,9601	-0,139	1,2585	0,6713	0,5266	0,4082
95	29	15	1,1858	0,9612	1,2578	0,6713	0,4318	0,4537
96	29	20	1,1304	0,6011	1,2574	0,5713	0,4222	0,4134
97	29	16	1,3395	1,5713	1,2565	0,6513	0,372	0,4795
98	29	20	1,0895	0,4411	1,2542	0,5713	0,4307	0,4058
99	29	11	1,1715	0,8912	1,2528	0,6513	0,4304	0,4411
100	29	14	1,3018	1,5013	1,2516	0,6713	0,3897	0,476
101	29	18	0,9673	-0,079	1,2514	0,6013	0,5132	0,3982
102	29	22	0,98	0,011	1,242	0,5512	0,4564	0,3613
103	29	21	1,3462	1,3213	1,2413	0,5512	0,3285	0,4386
104	29	20	1,201	0,8612	1,2407	0,5512	0,3951	0,4261
105	29	9	1,1374	0,6711	1,2396	0,5912	0,44	0,4161
106	29	19	1,22	0,9612	1,2367	0,5612	0,3992	0,4393
107	29	18	1,1066	0,5411	1,2303	0,5712	0,4582	0,4259
108	29	16	1,329	1,5313	1,2257	0,5912	0,3805	0,4777
109	29	12	1,0633	0,3911	1,225	0,6212	0,4891	0,4256
110	29	23	1,2299	0,8412	1,2216	0,5312	0,336	0,3873
111	29	16	1,3179	1,4913	1,2143	0,5712	0,3853	0,4757
112	29	20	0,9983	0,071	1,2121	0,5212	0,4738	0,3885
113	29	19	1,0835	0,4311	1,2111	0,5212	0,4521	0,414
114	29	16	1,0983	0,5411	1,2025	0,5512	0,4716	0,4342
115	29	19	1,2424	1,0512	1,2019	0,5112	0,3966	0,4433
116	29	17	1,0198	0,161	1,1955	0,5312	0,5014	0,4145
117	29	10	1,3517	1,6014	1,1933	0,5312	0,3667	0,4651
118	29	7	1,0607	0,3111	1,1878	0,4912	0,4566	0,3729
119	29	17	1,1952	0,9412	1,1878	0,5112	0,4282	0,4487
120	29	17	1,1952	0,9412	1,1878	0,5112	0,4282	0,4487
121	29	17	1,1952	0,9412	1,1878	0,5112	0,4282	0,4487
122	29	13	1,1819	0,9712	1,1835	0,5412	0,4405	0,4521
123	29	16	1,2614	1,2513	1,1804	0,5112	0,4097	0,4654
124	29	13	1,274	1,3913	1,1797	0,5312	0,4108	0,4694

No	COUNT	SCORE	INFIT MNSQ	INFIT ZSTD	OUTFIT MNSQ	OUTFIT ZSTD	PTMA	RMSR
125	29	15	1,1525	0,8012	1,1791	0,5212	0,4526	0,4473
126	29	11	1,0123	0,131	1,1774	0,5112	0,4977	0,41
127	29	9	1,0604	0,3411	1,1733	0,4812	0,4748	0,4018
128	29	17	1,2328	1,0912	1,173	0,4912	0,4165	0,4557
129	29	13	0,9992	0,061	1,1609	0,4912	0,5124	0,4157
130	29	13	1,149	0,8111	1,1581	0,4912	0,4547	0,4458
131	29	16	1,2723	1,3013	1,1565	0,4712	0,4092	0,4674
132	29	14	1,0915	0,5311	1,1553	0,4812	0,4761	0,4358
133	29	11	1,091	0,5111	1,1535	0,4712	0,4765	0,4256
134	29	23	1,0127	0,141	1,1514	0,4512	0,4295	0,3514
135	29	22	0,9946	0,071	1,1507	0,4412	0,4517	0,364
136	29	11	1,1629	0,8512	1,1505	0,4612	0,4458	0,4394
137	29	20	0,8512	-0,5691	1,1443	0,4311	0,5332	0,3587
138	29	22	1,255	0,9713	1,1432	0,4311	0,3519	0,4089
139	29	22	1,255	0,9713	1,1432	0,4311	0,3519	0,4089
140	29	16	1,2217	1,0812	1,1396	0,4411	0,4284	0,458
141	29	16	1,2268	1,1112	1,1393	0,4411	0,4278	0,4589
142	29	11	1,1466	0,7811	1,1388	0,4411	0,4529	0,4363
143	29	20	1,0816	0,4111	1,1343	0,4211	0,456	0,4044
144	29	20	1,2798	1,1413	1,1318	0,4111	0,3812	0,4398
145	29	19	1,1373	0,6411	1,1276	0,4011	0,4461	0,4241
146	29	12	1,0608	0,3711	1,1237	0,4111	0,4883	0,4251
147	29	22	1,101	0,4511	1,1217	0,4111	0,4131	0,383
148	29	19	1,2384	1,0312	1,1176	0,3911	0,4104	0,4426
149	29	13	1,134	0,7411	1,1104	0,3911	0,4656	0,4429
150	29	14	1,2101	1,0912	1,1086	0,3811	0,4417	0,4589
151	29	21	1,1472	0,6411	1,1033	0,3911	0,4128	0,4049
152	29	19	1,1715	0,7812	1,1027	0,3711	0,4333	0,4304
153	29	18	1,2451	1,1012	1,1008	0,3611	0,4161	0,4518
154	29	20	1,2438	1,0112	1,096	0,3711	0,3998	0,4336
155	29	16	1,1403	0,7311	1,0927	0,3511	0,4631	0,4425
156	29	18	1,1204	0,6011	1,0917	0,3511	0,4593	0,4286
157	29	13	1,2136	1,1212	1,0892	0,3411	0,4409	0,4582
158	29	15	1,18	0,9312	1,0874	0,3411	0,4529	0,4526
159	29	20	1,1284	0,5911	1,076	0,3411	0,4423	0,413
160	29	13	1,1441	0,7911	1,0757	0,3111	0,4694	0,4448
161	29	19	1,0179	0,151	1,0734	0,3211	0,4923	0,4012
162	29	18	1,035	0,231	1,0733	0,3211	0,4937	0,4119
163	29	22	1,3596	1,3014	1,0722	0,3511	0,3292	0,4256
164	29	20	0,9934	0,051	1,0688	0,3311	0,4876	0,3875
165	29	20	1,2746	1,1213	1,0682	0,3311	0,3927	0,439
166	29	16	1,2089	1,0312	1,0624	0,2911	0,4442	0,4556
167	29	23	1,1815	0,6912	1,061	0,3411	0,3704	0,3796
168	29	22	1,2411	0,9312	1,0561	0,3311	0,3722	0,4066
169	29	16	1,0727	0,4211	1,0553	0,2711	0,4927	0,4291
170	29	14	1,0934	0,5411	1,0498	0,261	0,4898	0,4362
171	29	18	1,0445	0,271	1,0461	0,271	0,4935	0,4138
172	29	24	1,0906	0,3811	1,0403	0,331	0,374	0,3445
173	29	15	0,9863	0,001	1,0379	0,231	0,5309	0,4137
174	29	18	1,1639	0,7812	1,0316	0,251	0,4545	0,4368
175	29	21	1,0784	0,3911	1,0309	0,291	0,4472	0,3925
176	29	16	1,1678	0,8512	1,0291	0,221	0,4629	0,4478
177	29	21	1,1094	0,5011	1,0289	0,291	0,4369	0,3981
178	29	14	1,0775	0,4611	1,0239	0,201	0,5003	0,433
179	29	16	1,1453	0,7511	1,022	0,211	0,4715	0,4434
180	29	21	1,0469	0,271	1,0201	0,281	0,4604	0,3868
181	29	15	1,1155	0,6311	1,0199	0,201	0,4839	0,44
182	29	21	1,1235	0,5511	1,0191	0,281	0,4338	0,4007
183	29	20	1,0495	0,281	1,0167	0,261	0,4765	0,3983
184	29	14	1,1516	0,8212	1,0149	0,181	0,4734	0,4477
185	29	16	1,076	0,4311	1,0146	0,191	0,4952	0,4298
186	29	25	1,2328	0,7212	1,0143	0,341	0,3071	0,3396
187	29	18	0,8765	-0,5091	1,0136	0,211	0,5662	0,379

No	COUNT	SCORE	INFIT MNSQ	INFIT ZSTD	OUTFIT MNSQ	OUTFIT ZSTD	PTMA	RMSR
188	29	15	1,0674	0,4011	1,0089	0,171	0,5019	0,4304
189	29	19	0,8836	-0,4491	1,0084	0,221	0,5469	0,3738
190	29	16	1,1024	0,5511	1,0046	0,171	0,4893	0,435
191	29	8	1,3483	1,3713	1,0032	0,211	0,384	0,4385
192	29	24	0,8646	-0,3491	1,0015	0,291	0,466	0,3067
193	29	17	1,0745	0,4111	1,0013	0,181	0,4939	0,4254
194	29	17	1,0828	0,4511	1,0011	0,181	0,4929	0,4271
195	29	16	1,0912	0,5011	1,0008	0,161	0,4933	0,4328
196	29	19	1,1555	0,7212	0,9957	0,201	0,4526	0,4275
197	29	18	1,1157	0,5811	0,9957	0,181	0,4743	0,4277
198	29	19	1,0531	0,3011	0,9956	0,201	0,4876	0,4081
199	29	23	1,0157	0,151	0,9929	0,251	0,4397	0,3519
200	29	9	0,8609	-0,5791	0,9901	0,171	0,5679	0,362
201	29	17	1,0778	0,4311	0,9899	0,161	0,4963	0,4261
202	29	17	1,0597	0,3511	0,986	0,151	0,5024	0,4225
203	29	17	1,1155	0,5911	0,9856	0,151	0,4821	0,4335
204	29	21	1,151	0,6512	0,9844	0,231	0,4284	0,4055
205	29	14	1,0643	0,3911	0,984	0,111	0,5074	0,4304
206	29	19	1,2222	0,9712	0,9786	0,181	0,4341	0,4397
207	29	16	1,0284	0,211	0,9717	0,101	0,52	0,4202
208	29	21	0,8948	-0,3491	0,97	0,211	0,522	0,3576
209	29	17	1,0534	0,3211	0,9677	0,111	0,5075	0,4212
210	29	21	1,0754	0,3711	0,9674	0,211	0,4554	0,392
211	29	14	1,0895	0,5211	0,9632	0,061	0,5018	0,4354
212	29	20	1,0303	0,201	0,9626	0,181	0,4904	0,3946
213	29	15	0,8633	-0,6591	0,9575	0,061	0,5838	0,3871
214	29	18	1,0693	0,3811	0,9527	0,111	0,4958	0,4187
215	29	19	1,1079	0,5311	0,9509	0,131	0,4749	0,4186
216	29	20	1,1564	0,6912	0,9509	0,171	0,4494	0,4181
217	29	16	1,0919	0,5111	0,9503	0,061	0,5001	0,433
218	29	23	0,9458	-0,0991	0,9463	0,1909	0,4596	0,3396
219	29	19	1,0156	0,141	0,9452	0,1209	0,5064	0,4008
220	29	17	0,9622	-0,109	0,9443	0,0709	0,541	0,4026
221	29	16	1,0109	0,121	0,9384	0,0309	0,5291	0,4166
222	29	18	1,0919	0,4811	0,9333	0,0709	0,4912	0,4231
223	29	22	1,1486	0,6211	0,9309	0,1609	0,4173	0,3912
224	29	25	1,1033	0,4011	0,9292	0,2509	0,3411	0,3212
225	29	19	1,1104	0,5411	0,9263	0,0909	0,4782	0,4191
226	29	18	1,0612	0,3411	0,9255	0,0609	0,5025	0,4171
227	29	18	0,9623	-0,099	0,9243	0,0609	0,5351	0,3972
228	29	24	1,1141	0,4511	0,9232	0,1909	0,3788	0,3482
229	29	17	1,0822	0,4511	0,9225	0,0209	0,5025	0,427
230	29	15	1,0216	0,171	0,9218	-0,0191	0,5298	0,4211
231	29	23	0,9426	-0,1091	0,9209	0,1609	0,4701	0,339
232	29	21	1,1059	0,4911	0,9193	0,1509	0,4536	0,3975
233	29	15	1,0275	0,201	0,9189	-0,0291	0,5292	0,4223
234	29	18	1,0619	0,3511	0,9187	0,0509	0,503	0,4172
235	29	24	1,2493	0,8412	0,9173	0,1809	0,3356	0,3687
236	29	21	1,0099	0,121	0,9075	0,1309	0,4874	0,3799
237	29	13	1,0012	0,071	0,9059	-0,0691	0,5391	0,4161
238	29	17	1,0356	0,241	0,9036	-0,0191	0,5216	0,4177
239	29	14	0,9941	0,031	0,9014	-0,0791	0,5437	0,4159
240	29	22	1,1531	0,6312	0,9007	0,1209	0,4207	0,3919
241	29	14	1,0484	0,311	0,8992	-0,0891	0,5254	0,4271
242	29	11	0,915	-0,3791	0,8985	-0,0691	0,5663	0,3898
243	29	15	1,0751	0,4411	0,8958	-0,0791	0,5167	0,432
244	29	13	0,9673	-0,109	0,8921	-0,1091	0,5542	0,409
245	29	22	1,0084	0,121	0,8894	0,1009	0,474	0,3665
246	29	18	0,993	0,041	0,8892	-0,0091	0,5318	0,4035
247	29	16	0,956	-0,149	0,8876	-0,0791	0,5546	0,4051
248	29	20	1,0852	0,4211	0,8863	0,0709	0,4792	0,405
249	29	17	1,0282	0,201	0,8834	-0,0591	0,5262	0,4162
250	29	20	0,9744	-0,029	0,883	0,0609	0,5159	0,3838

No	COUNT	SCORE	INFIT MNSQ	INFIT ZSTD	OUTFIT MNSQ	OUTFIT ZSTD	PTMA	RMSR
251	29	22	0,885	-0,3591	0,8827	0,0909	0,5181	0,3434
252	29	19	1,0185	0,161	0,8798	0,0109	0,5138	0,4013
253	29	21	1,0713	0,3611	0,8794	0,0909	0,4705	0,3912
254	29	17	0,9811	-0,019	0,8696	-0,0891	0,5444	0,4065
255	29	16	0,9688	-0,089	0,8656	-0,1291	0,553	0,4078
256	29	23	0,9287	-0,1591	0,8651	0,0809	0,4854	0,3365
257	29	15	0,9411	-0,2391	0,8615	-0,1591	0,5652	0,4042
258	29	16	0,9417	-0,2191	0,8591	-0,1391	0,5638	0,4021
259	29	11	1,1298	0,7011	0,8585	-0,1591	0,4964	0,4331
260	29	19	0,9756	-0,029	0,8539	-0,0291	0,5329	0,3928
261	29	16	0,9076	-0,3991	0,8536	-0,1491	0,5777	0,3947
262	29	15	0,8963	-0,4791	0,8497	-0,1892	0,5832	0,3944
263	29	16	0,9781	-0,039	0,8496	-0,1592	0,5527	0,4098
264	29	18	1,0304	0,211	0,8494	-0,0892	0,5242	0,411
265	29	16	0,9698	-0,079	0,849	-0,1592	0,5555	0,408
266	29	21	0,8422	-0,5692	0,8418	0,0308	0,557	0,3469
267	29	20	1,1169	0,5511	0,8402	0,0008	0,4771	0,4109
268	29	18	0,9788	-0,019	0,8399	-0,0992	0,5423	0,4006
269	29	16	0,9641	-0,109	0,8397	-0,1892	0,5587	0,4068
270	29	13	1,0557	0,3511	0,8394	-0,2392	0,5302	0,4273
271	29	21	0,9711	-0,029	0,8348	0,0208	0,5108	0,3725
272	29	21	0,9862	0,031	0,8343	0,0208	0,5029	0,3754
273	29	24	1,0635	0,3011	0,8323	0,0808	0,4053	0,3402
274	29	20	0,9351	-0,1891	0,832	-0,0192	0,5366	0,376
275	29	17	0,9137	-0,3491	0,8298	-0,1692	0,5721	0,3923
276	29	24	1,0021	0,111	0,8289	0,0708	0,4242	0,3302
277	29	2	1,4408	0,8214	0,8263	0,3408	0,2899	0,2599
278	29	19	1,1006	0,5011	0,8232	-0,0892	0,4978	0,4172
279	29	15	0,908	-0,4191	0,823	-0,2592	0,5827	0,397
280	29	22	1,0212	0,171	0,8224	0,0008	0,4736	0,3688
281	29	17	0,9598	-0,119	0,8213	-0,1892	0,5582	0,4021
282	29	26	0,9529	0,031	0,817	0,2208	0,361	0,2686
283	29	14	0,9535	-0,179	0,8164	-0,2892	0,5694	0,4073
284	29	21	0,9397	-0,1591	0,8152	0,0008	0,5236	0,3664
285	29	14	0,933	-0,2891	0,811	-0,3092	0,5766	0,4029
286	29	13	0,915	-0,3991	0,8102	-0,3092	0,5826	0,3978
287	29	17	0,9218	-0,3091	0,8094	-0,2092	0,573	0,394
288	29	13	0,9941	0,031	0,8079	-0,3192	0,5549	0,4147
289	29	22	0,9698	-0,029	0,8056	-0,0192	0,4938	0,3594
290	29	15	0,9052	-0,4291	0,8039	-0,2992	0,5859	0,3964
291	29	17	0,8586	-0,6291	0,8034	-0,2292	0,5959	0,3803
292	29	19	0,9248	-0,2591	0,8031	-0,1192	0,5572	0,3825
293	29	22	1,0505	0,2711	0,8001	-0,0292	0,4681	0,3741
294	29	21	0,8507	-0,5391	0,7991	-0,0292	0,557	0,3486
295	29	16	0,9527	-0,169	0,7968	-0,2892	0,569	0,4044
296	29	21	0,9046	-0,2991	0,7954	-0,0292	0,5374	0,3595
297	29	15	0,9201	-0,3491	0,7949	-0,3292	0,5824	0,3996
298	29	12	1,0078	0,101	0,7937	-0,3392	0,5498	0,4143
299	29	6	0,9348	-0,1091	0,7933	-0,0092	0,5212	0,3317
300	29	13	0,8774	-0,6091	0,7927	-0,3592	0,5977	0,3896
301	29	22	1,0328	0,211	0,7898	-0,0392	0,4767	0,3709
302	29	14	0,8569	-0,7191	0,7895	-0,3592	0,607	0,3861
303	29	18	0,9871	0,021	0,7892	-0,2092	0,5482	0,4023
304	29	14	0,8816	-0,5791	0,7889	-0,3592	0,5978	0,3917
305	29	16	0,9079	-0,3991	0,7827	-0,3192	0,5859	0,3948
306	29	16	0,8291	-0,8192	0,7823	-0,3192	0,6144	0,3773
307	29	19	1,0122	0,131	0,7812	-0,1592	0,5319	0,4001
308	29	19	0,9195	-0,2791	0,7769	-0,1692	0,5623	0,3813
309	29	13	0,863	-0,6891	0,7752	-0,4092	0,6049	0,3864
310	29	17	0,9076	-0,3791	0,7733	-0,2892	0,5831	0,391
311	29	19	1,0082	0,111	0,7707	-0,1792	0,5348	0,3993
312	29	18	0,9331	-0,2291	0,7669	-0,2492	0,5684	0,3911
313	29	22	1,0463	0,261	0,7631	-0,0892	0,4752	0,3733

No	COUNT	SCORE	INFIT MNSQ	INFIT ZSTD	OUTFIT MNSQ	OUTFIT ZSTD	PTMA	RMSR
314	29	17	0,7922	-0,9792	0,7593	-0,3292	0,6244	0,3653
315	29	13	0,8387	-0,8392	0,7578	-0,4492	0,6154	0,3809
316	29	17	0,8785	-0,5291	0,7569	-0,3292	0,5948	0,3847
317	29	17	0,9148	-0,3391	0,7552	-0,3392	0,5835	0,3925
318	29	11	0,9732	-0,069	0,7551	-0,4092	0,5628	0,402
319	29	23	0,8252	-0,5492	0,7548	-0,0792	0,5295	0,3172
320	29	18	0,9491	-0,1591	0,7537	-0,2792	0,5657	0,3944
321	29	25	1,1194	0,4411	0,7532	0,0408	0,3684	0,3236
322	29	16	0,8093	-0,9292	0,7516	-0,3992	0,6235	0,3727
323	29	19	0,9155	-0,2991	0,7508	-0,2192	0,567	0,3805
324	29	18	0,8898	-0,4391	0,749	-0,2893	0,5856	0,3819
325	29	18	0,8306	-0,7392	0,7477	-0,2893	0,6053	0,369
326	29	21	0,9615	-0,069	0,7468	-0,1093	0,5247	0,3707
327	29	20	0,8738	-0,4591	0,7465	-0,1593	0,5694	0,3634
328	29	16	0,8971	-0,4591	0,7462	-0,4093	0,5952	0,3924
329	29	23	1,0096	0,131	0,7451	-0,0893	0,467	0,3509
330	29	22	0,9692	-0,029	0,741	-0,1193	0,5022	0,3593
331	29	18	0,9325	-0,2391	0,7393	-0,3093	0,5733	0,391
332	29	11	0,7869	-1,0992	0,7378	-0,4593	0,6291	0,3615
333	29	17	0,8852	-0,4891	0,736	-0,3793	0,5959	0,3861
334	29	17	0,9063	-0,3791	0,7336	-0,3893	0,5895	0,3907
335	29	17	0,9063	-0,3791	0,7336	-0,3893	0,5895	0,3907
336	29	14	0,7334	-1,4693	0,7322	-0,5193	0,6577	0,3572
337	29	15	0,8995	-0,4591	0,7318	-0,4893	0,599	0,3951
338	29	13	0,9164	-0,3891	0,7272	-0,5393	0,5932	0,3981
339	29	18	0,9138	-0,3291	0,7265	-0,3393	0,5812	0,387
340	29	20	0,9667	-0,059	0,7243	-0,1993	0,5425	0,3823
341	29	24	1,0503	0,2611	0,722	-0,0793	0,4286	0,3381
342	29	16	0,848	-0,7192	0,7206	-0,4693	0,615	0,3815
343	29	21	1,0366	0,231	0,7204	-0,1493	0,506	0,3849
344	29	21	0,9396	-0,1591	0,72	-0,1493	0,5358	0,3664
345	29	12	0,8433	-0,7992	0,7199	-0,5393	0,6157	0,379
346	29	17	0,8529	-0,6591	0,7177	-0,4193	0,6092	0,379
347	29	21	0,9641	-0,059	0,7165	-0,1593	0,5284	0,3712
348	29	20	0,9531	-0,119	0,7143	-0,2093	0,5485	0,3796
349	29	4	0,9915	0,121	0,7139	0,0607	0,4812	0,2909
350	29	18	0,9068	-0,3591	0,7136	-0,3693	0,5857	0,3855
351	29	22	1,0533	0,2811	0,7136	-0,1693	0,4818	0,3746
352	29	18	0,8226	-0,7792	0,7135	-0,3693	0,6127	0,3672
353	29	18	0,8226	-0,7792	0,7135	-0,3693	0,6127	0,3672
354	29	15	0,8474	-0,7492	0,7118	-0,5393	0,6193	0,3835
355	29	22	0,7594	-0,8892	0,7076	-0,1793	0,5803	0,3181
356	29	21	0,9604	-0,069	0,7074	-0,1693	0,5312	0,3704
357	29	17	0,8572	-0,6391	0,7069	-0,4493	0,6094	0,38
358	29	23	0,9178	-0,1991	0,7066	-0,1493	0,5001	0,3345
359	29	18	0,7037	-1,4193	0,7058	-0,3793	0,6561	0,3396
360	29	21	0,8969	-0,3391	0,7051	-0,1793	0,5521	0,358
361	29	20	0,8568	-0,5391	0,7051	-0,2293	0,5806	0,3599
362	29	25	0,9126	-0,1291	0,7024	-0,0193	0,4372	0,2922
363	29	18	0,7815	-0,9892	0,702	-0,3893	0,6284	0,3579
364	29	19	0,894	-0,3991	0,701	-0,3193	0,5816	0,376
365	29	18	0,8724	-0,5291	0,6958	-0,3993	0,5993	0,3782
366	29	19	0,8805	-0,4591	0,6953	-0,3293	0,587	0,3732
367	29	17	0,8422	-0,7092	0,6881	-0,4893	0,6174	0,3766
368	29	21	0,9532	-0,099	0,6876	-0,2093	0,5363	0,3691
369	29	16	0,8255	-0,8392	0,6863	-0,5593	0,6275	0,3765
370	29	18	0,8198	-0,7892	0,6862	-0,4293	0,6174	0,3666
371	29	19	0,8844	-0,4391	0,6854	-0,3493	0,5872	0,374
372	29	19	0,8723	-0,4991	0,6853	-0,3493	0,5913	0,3714
373	29	18	0,8635	-0,5691	0,6828	-0,4293	0,6043	0,3762
374	29	18	0,8635	-0,5691	0,6828	-0,4293	0,6043	0,3762
375	29	24	0,8643	-0,3491	0,6788	-0,1393	0,4932	0,3067
376	29	15	0,8327	-0,8392	0,6774	-0,6393	0,6292	0,3802

No	COUNT	SCORE	INFIT MNSQ	INFIT ZSTD	OUTFIT MNSQ	OUTFIT ZSTD	PTMA	RMSR
377	29	19	0,7829	-0,9392	0,6763	-0,3693	0,6208	0,3519
378	29	21	0,8193	-0,6792	0,6754	-0,2293	0,5804	0,3422
379	29	16	0,8072	-0,9492	0,6726	-0,5993	0,636	0,3722
380	29	24	1,1274	0,4911	0,6659	-0,1593	0,4137	0,3503
381	29	20	0,8373	-0,6292	0,6649	-0,2993	0,5926	0,3558
382	29	15	0,8097	-0,9692	0,6648	-0,6693	0,6386	0,3749
383	29	23	0,9885	0,061	0,6641	-0,2193	0,4846	0,3472
384	29	18	0,7894	-0,9492	0,6631	-0,4793	0,6308	0,3597
385	29	18	0,7894	-0,9492	0,6631	-0,4793	0,6308	0,3597
386	29	14	0,7537	-1,3392	0,6616	-0,7193	0,6586	0,3622
387	29	24	0,8228	-0,4892	0,6572	-0,1793	0,5089	0,2992
388	29	21	0,8913	-0,3591	0,6545	-0,2593	0,5608	0,3569
389	29	18	0,7926	-0,9292	0,6534	-0,4993	0,6313	0,3605
390	29	14	0,7395	-1,4293	0,6531	-0,7393	0,6644	0,3587
391	29	19	0,8513	-0,5991	0,6505	-0,4193	0,6035	0,3669
392	29	23	0,9053	-0,2491	0,6486	-0,2494	0,5116	0,3322
393	29	16	0,8072	-0,9492	0,6423	-0,6794	0,6408	0,3723
394	29	19	0,7422	-1,1493	0,6396	-0,4394	0,6403	0,3426
395	29	20	0,8508	-0,5691	0,6394	-0,3494	0,5921	0,3586
396	29	16	0,7945	-1,0192	0,6363	-0,6994	0,6457	0,3693
397	29	20	0,8277	-0,6692	0,6349	-0,3594	0,6001	0,3537
398	29	16	0,7749	-1,1292	0,6337	-0,7094	0,6524	0,3647
399	29	16	0,7742	-1,1392	0,6323	-0,7094	0,6529	0,3646
400	29	12	0,8151	-0,9692	0,6316	-0,7994	0,6381	0,3726
401	29	18	0,7081	-1,3893	0,6307	-0,5494	0,6621	0,3407
402	29	15	0,7441	-1,3593	0,6298	-0,7794	0,6656	0,3594
403	29	20	0,8117	-0,7492	0,6294	-0,3694	0,6062	0,3503
404	29	20	0,8117	-0,7492	0,6294	-0,3694	0,6062	0,3503
405	29	16	0,7564	-1,2392	0,6291	-0,7194	0,6593	0,3604
406	29	15	0,733	-1,4293	0,6253	-0,7894	0,67	0,3567
407	29	15	0,7289	-1,4593	0,6248	-0,7894	0,6714	0,3557
408	29	20	0,8672	-0,4891	0,6241	-0,3794	0,5904	0,3621
409	29	17	0,7561	-1,1892	0,6231	-0,6594	0,6553	0,3569
410	29	16	0,7618	-1,2092	0,6216	-0,7394	0,6586	0,3616
411	29	19	0,8132	-0,7792	0,6215	-0,4794	0,6202	0,3586
412	29	21	0,8329	-0,6092	0,6213	-0,3194	0,5844	0,345
413	29	14	0,7522	-1,3492	0,6205	-0,8394	0,6646	0,3618
414	29	17	0,7884	-1,0092	0,6204	-0,6694	0,6457	0,3644
415	29	21	0,8684	-0,4591	0,6202	-0,3294	0,5739	0,3522
416	29	20	0,6852	-1,3793	0,6176	-0,3894	0,6497	0,3218
417	29	18	0,7427	-1,1993	0,6169	-0,5894	0,6529	0,3489
418	29	15	0,7783	-1,1592	0,6136	-0,8194	0,6571	0,3675
419	29	19	0,8071	-0,8092	0,6114	-0,4994	0,6239	0,3573
420	29	23	0,9247	-0,1691	0,6038	-0,3294	0,5134	0,3358
421	29	21	0,823	-0,6592	0,6004	-0,3594	0,5906	0,3429
422	29	18	0,6546	-1,7093	0,5979	-0,6294	0,6854	0,3276
423	29	16	0,7406	-1,3293	0,5973	-0,8094	0,6691	0,3566
424	29	22	0,8244	-0,6092	0,5965	-0,3694	0,57	0,3314
425	29	19	0,6072	-1,8994	0,5962	-0,5394	0,6917	0,3099
426	29	19	0,6072	-1,8994	0,5962	-0,5394	0,6917	0,3099
427	29	18	0,7392	-1,2193	0,5945	-0,6394	0,6577	0,3481
428	29	25	0,9519	-0,009	0,5944	-0,1694	0,4375	0,2984
429	29	20	0,7828	-0,8892	0,5928	-0,4394	0,6211	0,344
430	29	21	0,7873	-0,8192	0,5845	-0,3894	0,6047	0,3354
431	29	21	0,7821	-0,8492	0,5836	-0,3894	0,6064	0,3343
432	29	23	0,8528	-0,4491	0,5812	-0,3694	0,5405	0,3225
433	29	22	0,8096	-0,6692	0,5805	-0,3994	0,5775	0,3284
434	29	19	0,7334	-1,1893	0,5732	-0,5894	0,6527	0,3406
435	29	19	0,7006	-1,3693	0,5642	-0,6094	0,6645	0,3329
436	29	25	0,8878	-0,1991	0,5547	-0,2294	0,4631	0,2882
437	29	12	0,7087	-1,6293	0,5519	-1,0494	0,685	0,3474
438	29	21	0,7682	-0,9092	0,5487	-0,4595	0,6162	0,3313
439	29	20	0,7466	-1,0693	0,5455	-0,5395	0,6404	0,3359

No	COUNT	SCORE	INFIT MNSQ	INFIT ZSTD	OUTFIT MNSQ	OUTFIT ZSTD	PTMA	RMSR
440	29	23	0,7746	-0,7592	0,5421	-0,4395	0,5699	0,3073
441	29	23	0,7746	-0,7592	0,5421	-0,4395	0,5699	0,3073
442	29	18	0,6976	-1,4493	0,539	-0,7795	0,6802	0,3382
443	29	20	0,6832	-1,3893	0,539	-0,5495	0,6607	0,3214
444	29	13	0,6857	-1,7993	0,5354	-1,1295	0,6984	0,3444
445	29	19	0,6895	-1,4293	0,535	-0,6795	0,6728	0,3302
446	29	21	0,7313	-1,0893	0,5346	-0,4895	0,6296	0,3233
447	29	21	0,7596	-0,9492	0,5316	-0,4895	0,6218	0,3294
448	29	19	0,6949	-1,3993	0,5295	-0,6895	0,6722	0,3315
449	29	17	0,6453	-1,8494	0,5291	-0,9195	0,7056	0,3297
450	29	23	0,7684	-0,7892	0,5222	-0,4795	0,5747	0,3061
451	29	21	0,7283	-1,0993	0,5208	-0,5095	0,6331	0,3226
452	29	21	0,7198	-1,1393	0,5203	-0,5195	0,6356	0,3207
453	29	17	0,645	-1,8494	0,5185	-0,9495	0,7074	0,3296
454	29	21	0,7317	-1,0793	0,5156	-0,5295	0,633	0,3233
455	29	26	1,1577	0,4912	0,5149	-0,1295	0,3478	0,2961
456	29	21	0,7254	-1,1193	0,509	-0,5395	0,6361	0,3219
457	29	22	0,741	-0,9793	0,5074	-0,5395	0,6108	0,3142
458	29	22	0,7174	-1,0893	0,5045	-0,5495	0,6186	0,3091
459	29	24	0,822	-0,4992	0,5043	-0,4295	0,5294	0,2991
460	29	19	0,6591	-1,5993	0,5013	-0,7595	0,688	0,3229
461	29	21	0,7004	-1,2393	0,4996	-0,5595	0,6451	0,3164
462	29	18	0,6041	-2,0194	0,4989	-0,8895	0,7159	0,3147
463	29	22	0,7474	-0,9493	0,4985	-0,5595	0,61	0,3155
464	29	20	0,6445	-1,5994	0,4964	-0,6495	0,6796	0,3121
465	29	19	0,6499	-1,6494	0,4917	-0,7895	0,6926	0,3206
466	29	17	0,6189	-2,0194	0,4903	-1,0295	0,7203	0,3229
467	29	22	0,7076	-1,1293	0,4851	-0,5895	0,6247	0,307
468	29	21	0,7025	-1,2293	0,4832	-0,5895	0,6476	0,3168
469	29	14	0,6137	-2,2794	0,4813	-1,3095	0,7317	0,3268
470	29	24	0,7605	-0,7192	0,4718	-0,4995	0,5528	0,2877
471	29	19	0,5905	-1,9994	0,4706	-0,8395	0,714	0,3056
472	29	20	0,6294	-1,6894	0,4671	-0,7095	0,6893	0,3085
473	29	16	0,5906	-2,2994	0,4633	-1,2295	0,7389	0,3184
474	29	22	0,7135	-1,0993	0,4631	-0,6395	0,6267	0,3083
475	29	4	0,6808	-0,7193	0,463	-0,2695	0,6014	0,241
476	29	22	0,6814	-1,2593	0,4614	-0,6395	0,6364	0,3013
477	29	23	0,7145	-1,0093	0,4603	-0,6095	0,6005	0,2952
478	29	15	0,5817	-2,4494	0,4597	-1,3295	0,7449	0,3177
479	29	19	0,6093	-1,8894	0,4588	-0,8695	0,7107	0,3104
480	29	22	0,6659	-1,3293	0,4529	-0,6595	0,6424	0,2978
481	29	23	0,7363	-0,9193	0,4513	-0,6195	0,5959	0,2996
482	29	20	0,6026	-1,8394	0,4435	-0,7696	0,7015	0,3018
483	29	19	0,5485	-2,2695	0,4337	-0,9396	0,7333	0,2945
484	29	22	0,6537	-1,3893	0,4217	-0,7296	0,6517	0,2951
485	29	21	0,5826	-1,8594	0,4044	-0,7696	0,6972	0,2885
486	29	4	0,6544	-0,7993	0,3838	-0,3996	0,6204	0,2363
487	29	26	0,8213	-0,2892	0,3806	-0,3296	0,4606	0,2494
488	29	25	0,7652	-0,5892	0,3622	-0,5696	0,532	0,2675
489	29	24	0,6733	-1,0693	0,3495	-0,7597	0,6006	0,2707
490	29	25	0,7137	-0,7593	0,3437	-0,6097	0,5493	0,2584
491	29	2	1,237	0,5612	0,3374	-0,1697	0,4125	0,2408
492	29	24	0,6332	-1,2394	0,3288	-0,8097	0,6157	0,2625
493	29	27	0,7656	-0,2692	0,3272	-0,2297	0,4181	0,2051
494	29	26	0,7543	-0,4692	0,3248	-0,4197	0,4904	0,239
495	29	23	0,5557	-1,7694	0,3193	-0,9397	0,6724	0,2603
496	29	23	0,5543	-1,7694	0,3186	-0,9397	0,673	0,26
497	29	24	0,5934	-1,4094	0,308	-0,8597	0,6308	0,2541
498	29	25	0,6478	-0,9994	0,303	-0,6997	0,5756	0,2461
499	29	21	0,4251	-2,8496	0,2996	-1,0497	0,7626	0,2465
500	29	2	0,5021	-0,7595	0,1378	-0,5499	0,6014	0,1534

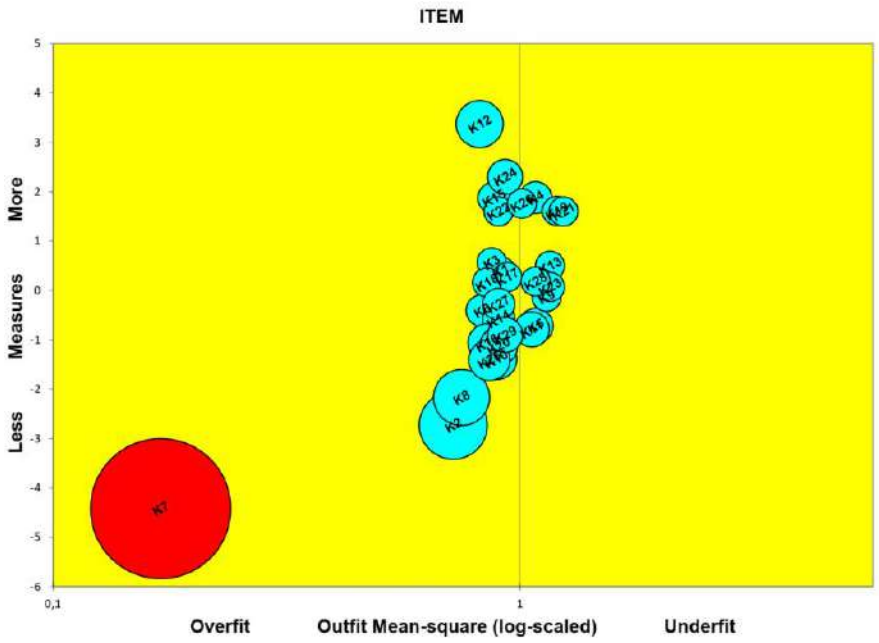
*MNSQ, mean-square; ZSTD, z-standard; PTMA, point measure correlation; RMSR, root-mean-square residual

Appendix D: Item fit measurement

ITEM	COUNT	INFIT MNSQ	INFIT ZSTD	OUTFIT MNSQ	OUTFIT ZSTD	PTMA	RMSR
K21	500	1,1638	3,8012	1,2445	2,8512	0,1619	0,4755
K19	500	1,1503	3,4912	1,1986	2,3312	0,1793	0,4721
K13	500	1,1529	4,4612	1,1593	2,8112	0,2149	0,4937
K23	500	1,1144	2,7411	1,1563	2,3812	0,2447	0,4664
K9	500	1,1034	2,2011	1,1448	1,9911	0,2528	0,4508
K28	500	1,0647	1,6811	1,0803	1,3311	0,3005	0,4619
K5	500	1,0362	0,561	1,0801	0,8111	0,3048	0,3881
K4	500	1,032	0,671	1,076	0,8111	0,282	0,4291
K11	500	1,0053	0,101	1,0617	0,6111	0,3313	0,3756
K26	500	1,0279	0,631	1,0112	0,161	0,3027	0,4369
K17	500	0,9612	-1,069	0,9373	-1,0891	0,4067	0,443
K24	500	0,9661	-0,519	0,9312	-0,5591	0,3308	0,3801
K29	500	0,9705	-0,379	0,9309	-0,5891	0,3763	0,3579
K1	500	0,9129	-2,6191	0,9087	-1,6791	0,4523	0,4363
K20	500	0,9644	-0,399	0,9042	-0,7291	0,3718	0,3348
K22	500	0,9299	-1,7391	0,9023	-1,2291	0,4082	0,4251
K27	500	0,946	-1,0791	0,8994	-1,3291	0,4189	0,4072
K14	500	0,9682	-0,509	0,8963	-1,1291	0,3947	0,3871
K10	500	0,9618	-0,359	0,8945	-0,6891	0,3655	0,3086
K15	500	0,9242	-1,5991	0,8848	-1,2291	0,4009	0,4068
K3	500	0,9201	-2,5491	0,8682	-2,5491	0,4538	0,4427
K25	500	0,9401	-0,5791	0,8596	-0,9291	0,3877	0,3031
K16	500	0,9432	-0,6791	0,8541	-1,2091	0,4043	0,3377
K18	500	0,8986	-2,7191	0,8531	-2,5391	0,4718	0,4234
K6	500	0,8963	-1,9591	0,8284	-2,1792	0,4665	0,3867
K12	500	1,0108	0,131	0,8185	-0,9492	0,2358	0,2812
K8	500	1,0622	0,4611	0,7538	-1,0992	0,3019	0,2464
K2	500	1,1571	0,8312	0,7245	-0,8993	0,2272	0,2072
K7	500	0,8134	-0,3392	0,1682	-2,1798	0,3391	0,0866

*K, knowledge item; MNSQ, mean-square; ZSTD, z-standard; PTMA, point measure correlation; RMSR, root-mean-square residual

Appendix E: Item Fit Order for all items in AKAQ with 29 items (including item K7)



Appendix F: Differential Item Functioning (DIF) by term

Name	DIF CONTRAST	JOIN S.E.	Mantel-Haenszel		Size	Active slices	Item number	DIF classification
			Chi-squ	Prob.	CUMLOR			
K1	.48	.20	35.676	.0589	.41	17	1	
K2	.15	.49	.0381	.8453	.25	17	2	
K3	-.11	.20	12.489	.2638	-.26	17	3	
K4	.21	.21	13.190	.2508	.26	17	4	
K5	.19	.24	15.371	.2150	.35	17	5	
K6	.79	.24	80.784	.0045	.75	17	6	moderate to large
K8	.38	.41	.5901	.4424	.46	17	8	
K9	-.09	.21	.1518	.6969	.10	17	9	
K10	.54	.31	17.219	.1894	.45	17	10	
K11	.20	.25	.6843	.4081	.24	17	11	
K12	-.24	.32	.8380	.3600	-.35	17	12	
K13	-.51	.20	23.627	.1243	-.32	17	13	
K14	.29	.24	12.883	.2564	.31	17	14	
K15	-.49	.21	71.371	.0076	-.67	17	15	
K16	-.34	.26	29.951	.0835	-.53	17	16	
K17	.26	.20	12.682	.2601	.26	17	17	
K18	.32	.21	.8260	.3634	.22	17	18	
K19	-.67	.21	54.267	.0198	-.50	17	19	moderate to large
K20	.18	.27	.1096	.7407	.14	17	20	
K21	.15	.20	.9444	.3312	.22	17	21	
K22	.00	.20	.0772	.7812	-.08	17	22	
K23	-.29	.20	.7477	.3872	-.20	17	23	
K24	.27	.23	10.753	.2997	.28	17	24	
K25	-.45	.29	30.927	.0786	-.61	17	25	
K26	-.24	.21	.9016	.3424	-.22	17	26	
K27	.00	.22	.1131	.7366	-.10	17	27	
K28	-.22	.20	.3108	.5772	-.13	17	28	
K29	-.18	.25	.5311	.4661	-.22	17	29	

*K, knowledge item; DIF, differential item functioning; DIF S.E., standard error of the differential item functioning; Chi-squ, chi-square; Prob., probability; CUMLOR, cumulative log-odds ratio in logits;

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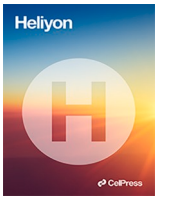

Research article

Favipiravir does not improve viral clearance in mild to moderate COVID-19 – A systematic review and meta-analysis of randomized controlled trials

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Favipiravir
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SARS-CoV-2
Efficacy
Meta-analysis

ABSTRACT

Purpose: Favipiravir has been used in the therapy of COVID-19, including patients with mild to moderate symptoms in certain countries. The aim of our systematic review and meta-analysis was to investigate its efficacy and safety in mild-to-moderate COVID-19 infections.
Methods: The PubMed, Embase, Web of Science, and Cochrane databases were systematically reviewed for articles reporting the results of randomized controlled trials published until January 6, 2023, resulting in the identification of 20 eligible studies.
Results: There were no significant differences in viral clearance time (HR = 1.20, p = 0.09) compared to those without favipiravir therapy. However, in the subgroup analyses, favipiravir treatment significantly increased viral clearance by 59 % (HR = 1.59, $p < 0.01$) and 42 % (HR = 1.42, $p < 0.01$], $I^2 = 20$ %) compared to the comparator group in patients with moderate severity of COVID-19 and in the inpatient care setting, respectively. Favipiravir had no beneficial effects in the case of patients with mild symptoms and treated in ambulatory care.
Conclusions: The use of favipiravir is questionable in the treatment of outpatients with COVID-19 with mild symptoms. Moderate beneficial effects in the case of patients with moderate symptoms and inpatients should be treated with care due to the limitations of the analysed trials.

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1. Introduction

Favipiravir, a broad-spectrum antiviral drug, was initially developed for treating influenza. It is phosphoribosylated to its active form, favipiravir-ribofuranosyl-5′-triphosphate, by cellular enzymes, and it inhibits the RNA-dependent RNA polymerase of the influenza virus, thereby it is used to decrease viral load. Favipiravir was approved as a treatment for novel or re-emerging influenza viruses in Japan in 2014. Based on its mechanism of action, it might be effective against other RNA viruses, e.g., Ebola virus, Lassa virus, and rabies [1]. After the outbreak of the COVID-19 pandemic, favipiravir was one of the candidates for antiviral therapy for this disease. However, favipiravir was not approved in countries other than Japan until March 2020, when it was officially recommended in China to treat COVID-19 infection. In June 2020, India also approved favipiravir with the same indication [2].

The clinical efficacy of favipiravir in COVID-19 infection was first studied in China however, these (and other early) studies had several weaknesses (e.g. lack of randomization and blinding, heterogenous study population) [3,4]. Later, the number of registered or published clinical trials increased rapidly, and favipiravir was authorized for emergency or compassionate use in several countries, including Bangladesh, Egypt, Hungary, Japan, Kazakhstan, Moldova, Russia, Saudi Arabia, Thailand, Turkey, Ukraine, United Arab Emirates, and Uzbekistan [5,6].

As other potentially effective antiviral agents appeared on the market or were subjected to clinical trials (e.g., remdesivir, molnupiravir, paxlovid) and the studies with favipiravir did not unequivocally support the efficacy of this pharmacon, the position of favipiravir changed in the majority of the therapeutic guidelines. Furthermore, favipiravir has remained unapproved by the Food and Drug Administration of the United States of America and the European Medicines Agency to treat COVID-19. Since the outbreak of the COVID-19 pandemic, several clinical trials have been conducted, and the efficacy of favipiravir has also been assessed in meta-analyses. However, previous meta-analyses did not assess the efficacy of favipiravir on viral clearance time as the primary outcome measure. Our aim was to systematically review the literature and analyse the clinical efficacy and safety of favipiravir in mild to moderate COVID-19.

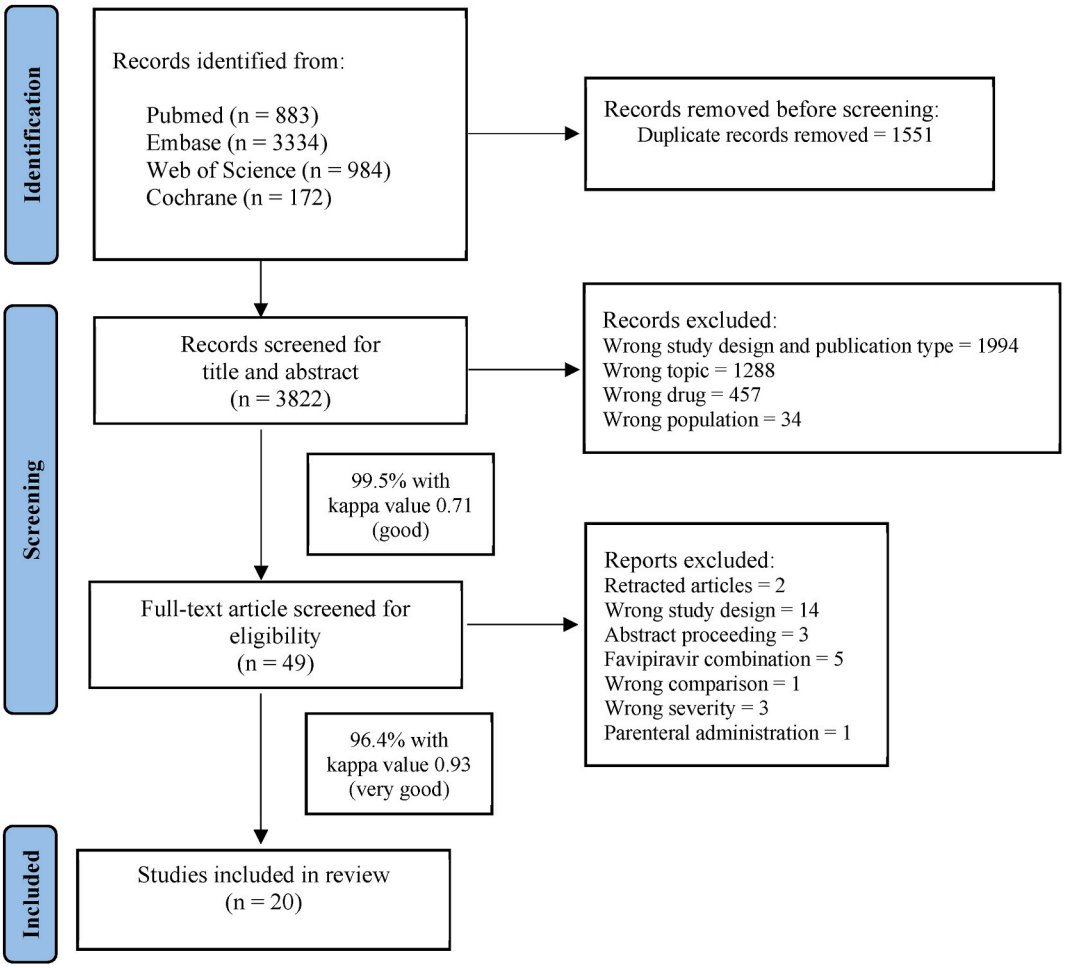

Fig. 1. Flow chart of study selection.

Table 1
Characteristics of eligible studies.

Ref.	Country	Study Design	Number of patients		Age			Sex (Male in %)	Severity	Setting of care	Favipiravir	Comparator	Onset to randomization
			Favipiravir (F)	Comparator (C)	Mean in years (SD)	Median in years (IQR)	Quantity (<65 years, %)						
Abdur Rahman, 2022[42]	Bangladesh	Double-blinded randomized controlled trial	25	25	F: 37.96 (11.45) C: 37.54 (10.18)			F: 64 C: 68	Mild and Moderate	Inpatient	1st day: 1600 mg (bid) 2nd – 10th day: 600 mg (bid)	Placebo	Within 7 days
AlQahtani, 2022[37]	Bahrain	Randomized, controlled, open-labeled study	54	51		F: 44.5 (33.0, 50.0) C: 48.5 (35.5, 57.0)		F: 43 C: 52	Mild and Moderate	Inpatient	1st day: 1600 mg (bid) 2nd – 10th day: 600 mg (bid)	SoC	Within 10 days
Balykova,2020a[38]	Russia	Randomized, open-label, multicenter comparative study	17	22	F: 47.1 (2.3) C: 47.5 (1.9)			No Information	Moderate	Inpatient	1st day: 1600 mg (bid) 2nd – 14th days: 600 mg (bid)	SoC treatment of COVID-19 in Russian guideline	Hospitalization not exceeding 48 h before administration of favipiravir
Balykova, 2020b[39]	Russia	Open randomized multicentre comparative study	100	100	Mean age of population: 49.7 (13.1) Range of age: 20 to 80			F: 50.9 C: 49.0	Moderate	Inpatient	1st day: 1600 mg (bid) 2nd – 14th day: 600 mg (bid)	SoC treatment of COVID-19 in Russian guideline	Hospitalized not more than 48 h before the start of the study
Bossaed, 2021[30]	Saudi Arabia	Randomized double-blinded, multicentre placebo-controlled trial	112	119		F: 37 (31.5, 45.0) C: 37 (32, 44)		F: 64.2 C: 69.7	Mild	Outpatient	1st day: 1800 mg (9 tab) (bid) 2nd – 5th or 7th days: 800 mg (bid)	SoC + Placebo	Within 5 days of disease onset
Chen, 2021[4]	China	Randomized controlled, open-label multicenter trial	116	120			F: 75 C: 65.8	F: 50.9 C: 42.5	Moderate	Inpatient	1st day: 1600 mg (bid) 2nd – 7th days: 600 mg (bid)	SoC + Umifenovir: 200 mg (tid)	Within 12 days of initial symptoms
Chuah, 2022[45]	Malaysia	Randomized, open-label, parallel, multicenter, phase 3 clinical trial	250	250	F: 62.6 (7.51) C: 62.4 (8.41)			F: 52.4 C: 44.4	Mild to moderate	Inpatient	1st day: 1800 mg (bid) 2nd – 5th days: 800 mg (bid)	SoC	Within 7 days
Golan, 2022[43]	USA, Brazil, Mexico	Randomized, multicenter, double-blinded, placebo-controlled trial	599	588			F (<60, %): 84.5 C (<60, %): 86.1	F: 47.1 C: 44.4	Mild to moderate	Outpatient	1st day: 1800 mg (bid) 2nd – 10th days: 800 mg (bid)	Placebo + SoC	Within 5 days
Holubar, 2021[31]	USA	Randomized, double-blind, placebo-	59	57	F: 42.9 (12.3) C: 43.4 (12.8)			F: 52.5 C: 49.1	Mild	Outpatient	1st day: 1800 mg (bid) 2nd – 10th	Placebo + SoC	Positive SARS-CoV2 RT-PCR

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Table 1 (*continued*)

Ref.	Country	Study Design	Number of patients		Age			Sex (Male in %)	Severity	Setting of care	Favipiravir	Comparator	Onset to randomization
			Favipiravir (F)	Comparator (C)	Mean in years (SD)	Median in years (IQR)	Quantity (<65 years, %)						
		controlled phase 2 trial									day: 800 mg (bid)		within 72 h of enrollment
Ivashchenko, 2020[40]	Russia	Randomized, adaptive, multicenter, open-label, Phase II/III clinical trial	40	20		No information		No information	Moderate	Inpatient	1st day: 1600 mg (bid) 2nd – 14th days: 600 mg (bid) or 1st day: 1800 mg (bid) 2nd – 14th day: 800 mg (bid)	SoC	No information
Lou, 2021[41]	China	Randomized, exploratory single-center, open-label, controlled trial	9	10	F: 58.0 (8.1) C: 46.6 (14.1)			F: 77 C: 70	Mild to Moderate	Inpatient	1st day: 1600 mg or 2200 mg (tid) 2nd – 14th days: 600 mg (tid)	SoC	No information
Lowe, 2022[28]	UK	Randomized, Double-blind, 2x2 factorial placebo-controlled trial	59	60	F: 40.3 (12.1) C: 40.6 (12.2)			F: 54.2 C: 51.7	Mild	Outpatient	1st day: 1800 mg (bid) 2nd – 7th day: 400 mg (qid)	Placebo + SoC	Within 7 days of symptom onset
McMahon, 2022[47]	Australia	Randomized placebo-controlled phase 2 trial	66	67		F: 36 (28–49) C: 35 (27.5, 52.5)		F: 55.6 C: 54	Mild and Moderate	Inpatient and Outpatient	1st day: 1800 mg (bid) 2nd – 14th day: 800 mg (bid)	Placebo + SoC	Within 5 days
Ruzhentsova, 2021[32]	Russia	Randomized, open-label, active-controlled trial	112	56	F: 41.7 (10.6) C: 42.0 (10.4)			F: 43.8 C: 53.6	Mild and Moderate	Inpatient and Outpatient	1st day: 1800 mg (bid), 2nd – 9th day: 800 mg (bid)	SoC	No more than 6 days
Shenoy, 2021[46]	Kuwait	Randomized, multicentre, double-blind, placebo-controlled, parallel design	175	178			F (<50, %): 40 C (<50, %): 41.6	F: 67.4 C: 67.4	Moderate	Inpatient	1st day: 1800 mg (bid), 2nd – 10th day: 800 mg (bid)	Placebo + SoC	Within 10 days
Shinkai, 2021[33]	Japan	Randomized, single-blind, placebo-controlled, parallel-group design	107	49	F: 43.8 (12.5) C: 48.7 (14.1)		F: 94.4 C: 85.7	F: 71.0 C: 57.1	Moderate	Inpatient	1st day: 1800 mg (bid) 2nd – 13th day: 800 mg (bid)	Placebo + SoC	Within 10 days
Sirijatuphat, 2022[36]	Thailand	Multicentre, open-labeled,	62	31		F: 32 (27–39)		F: 33.9 C: 38.7	Mild	Inpatient	1st day: 1800 mg (bid) 2nd – 14th	SoC	Within 10 days

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Table 1 (*continued*)

Ref.	Country	Study Design	Number of patients		Age			Sex (Male in %)	Severity	Setting of care	Favipiravir	Comparator	Onset to randomization
			Favipiravir (F)	Comparator (C)	Mean in years (SD)	Median in years (IQR)	Quantity (<65 years, %)						
		randomized control study				C: 28 (25, 35)					day: 800 mg (bid)		
Tehrani, 2022[44]	Iran	Randomized, open-label, controlled clinical trial,	38	40	F: 53.08 (11.80) C: 51.95 (13.34)			F: 52.6 C: 57.5	Moderate	Outpatient	1st day: 1600 mg (bid) 2nd – 4th day: 600 mg (bid)	SoC	Within 3–9 days
Udwadia, 2021[34]	India	Randomized, open-label, parallel-arm, multicenter trial	72	75	F: 43.6 (12.2) C: 43.0 (11.2)			F: 70.8 C: 76.0	Mild and Moderate	Inpatient	1st day: 1800 mg (bid), 2nd – 14th day: 800 mg (bid)	SoC	No more than 7 days
Zhao, 2021[35]	China	Multicenter open-label, randomized controlled trial	36	19	F: 55.8 (13.6) C: 55.5 (12.6)			F: 44.4 C: 47.4	Mild and Moderate	Inpatient	1st day: 1600 mg (bid) 2nd – 7th days: 600 mg (bid)	SoC	No information

SoC: standard of care; bid: two times per day; tid: three times a day; qid: four times per day.

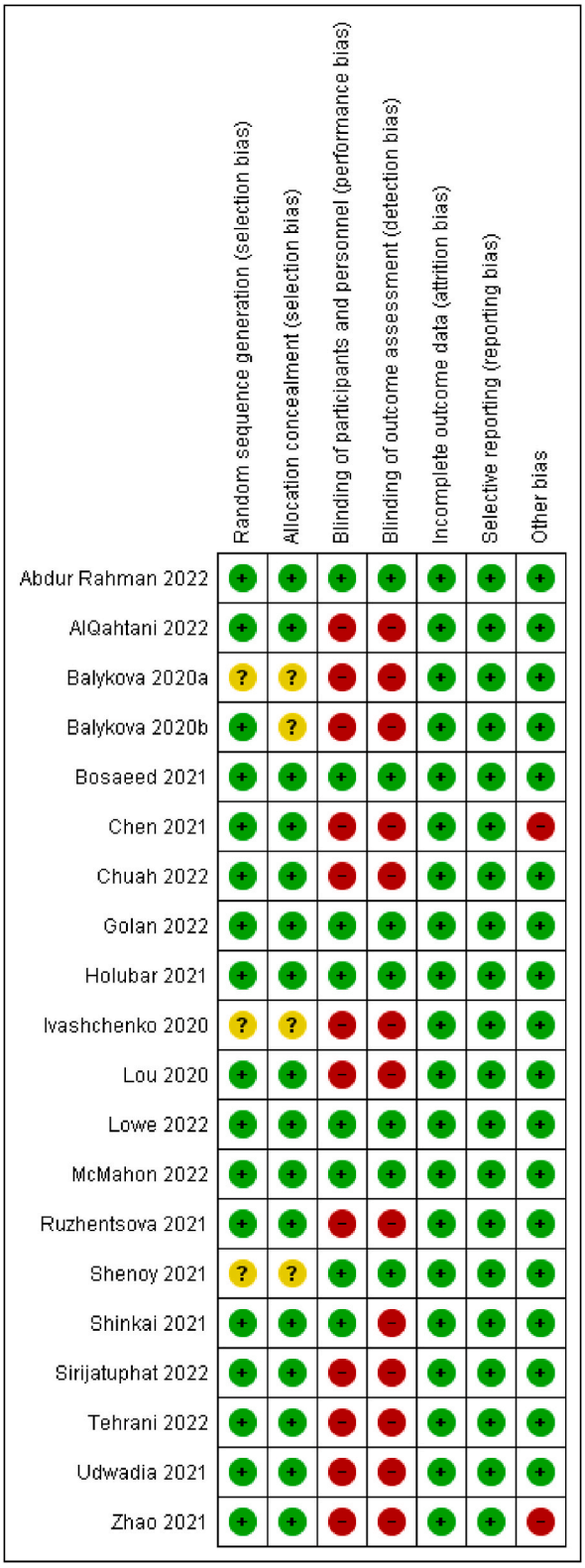

Fig. 2. Risk of bias summary of included studies.

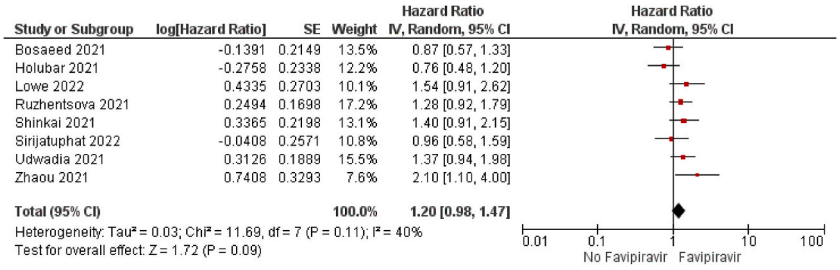

Fig. 3. Favipiravir has no significant effect on viral clearance compared to comparator.

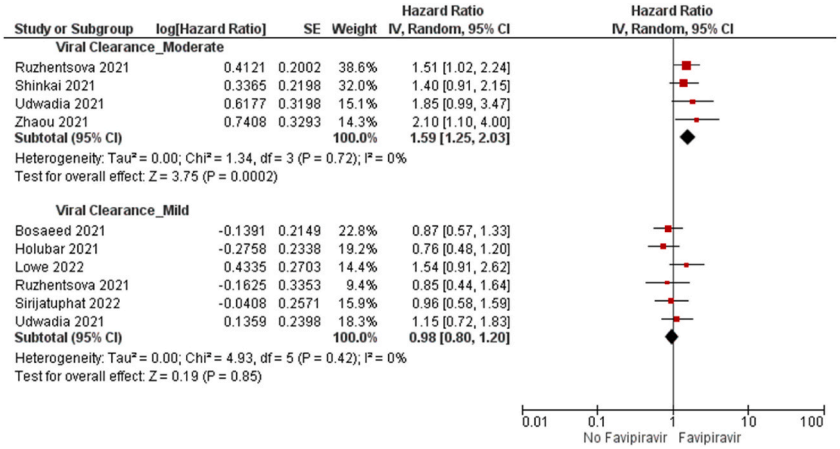

Fig. 4. Favipiravir is more effective in terms of viral clearance in moderate, but not in mild severity.

2. Methods

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement was used to guide the report of this meta-analysis [7]. The study protocol was prospectively registered in PROSPERO under the reference number CRD4202232443 (www.crd.york.ac.uk).

2.1. Inclusion criteria

The patient, intervention, comparison, outcomes, and study design (PICOS) approach was used to answer our clinical questions and applied as follows: P: COVID-19 patients with mild-to-moderate conditions (categorized by the authors of the trials), I: favipiravir, C: placebo/standard of care/another antiviral drug, O: time to viral clearance, S: randomized, controlled trials. The definition of mild and moderate illness in the papers is usually based on the descriptions provided by the World Health Organization (WHO) [8]. Mild patients were 'symptomatic patients (fever, cough, fatigue, shortness of breath, anorexia, etc) without viral pneumonia or hypoxia' and had no imaging findings of pneumonia. Meanwhile, moderate patients were 'patients with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) with no signs of severe pneumonia, including SpO2 $\geq$ 90 % on room air but had imaging findings on pneumonia. Viral clearance was defined as the change in the RT-PCR result from positive to negative in two consecutive tests separated by at least 24 h. Secondary outcomes were clinical recovery rates, the proportion of patients with improvement in chest imaging compared to baseline, death, emergency department visit, hospitalization, admission to the ICU and hospital discharge. Clinical recovery was defined as the improvement in the patient's clinical condition indicated by improvements in respiratory signs and symptoms (such as oxygen saturation, respiratory rate, chest imaging), normalization of body temperature, or improvement in other relevant clinical indicators (for example, WHO category of clinical status) sustained for at least 72 h. Indicators of safety included in this study were the proportion of patients who developed hyperuricemia, low hemoglobin, hyperglycemia, elevated levels of alanine transaminase (ALT) and aspartate aminotransferase (AST), high bilirubin, elevated creatine phosphokinase, high triglycerides, and leukopenia, as well as experiencing symptoms such as abdominal pain, anorexia, constipation, diarrhea, dizziness, dyspnoea, dyspepsia, headache, myalgia, nasal congestion, nausea, rhinorrhoea, skin rash, and vomiting.

Table 2
Effects of favipiravir on clinical improvement.

Reference	Parameters	Results		
		Overall	Mild	Moderate
Favorable for favipiravir (FPV)				
Balykova, 2020b[39]	The proportion of patients who achieved clinical scale ≤2 in the WHO 8-Category Ordinal Scale (transfer to outpatient or complete recovery)			RR: 1.34, 95 % CI: 1.15–1.56 FPV: 90 % SoC: 67 %
Chen, 2021[4]	Clinical recovery rate: based on the recovery of temperature, respiratory rate, oxygen saturation, and cough relief.			RR: 1.28, 95 % CI: 1.04–1.57 FPV: 71.43 % SoC + Umifenovir: 55.86 % Rate ratio: 0.1557 (95 % CI: 0.03–0.28, p value = 0.02)
Ruzhentsova, 2021[32]	Time to a reduction of patient clinical status on at least 1 score according to the WHO 8-Category Ordinal Scale compared to baseline.	HR: 1.63, 95 % CI: 1.14–2.34 Median time FPV: 6 days (IQR: 4–9.25 days) SoC: 10 days (IQR: 5–21 days) RR: 1.26, 95 % CI: 1.02–1.54 FPV: 83.03 % SoC: 66.10 %		HR: 1.66, 95 % CI: 1.09–2.52
Shinkai, 2021[33]	Time to improvement in four clinical parameters: temperature, SpO_2, chest imaging, and viral clearance (two consecutive negative results separated by at least 24 h).			HR: 1.59, 95 % CI: 1.02–2.48 Median time FPV: 11.9 days (95 % CI: 10.0–13.1) Placebo: 14.7 days (95 % CI: 10.5–17.9) RR: 1.32, 95 % CI: 1.02–1.73 FPV: 75.70 % SoC: 57 %
Sirijatuphat, 2022[36]	Time to sustained clinical improvement by a National Early Warning Score (NEWS) of ≤1 for at least 7 days		HR: 2.77, 95 % CI: 1.57–4.88 Median time FPV: 2 days Control: 14 days Range of 1–28 days for both groups RR: 2.45, 95 % CI: 1.45–4.15 FPV: 79 % SoC: 32.3 %	
Tehrani, 2022[44]	Respiratory rate at the end of study (day 7 after treatment)	F: 21.08 ± 2.92 SoC: 19.3 ± 1.60 P < 0.01		
Udwadia, 2021[34]	Time to clinical cure: according to clinician assessment and clinical parameters such as normalization of fever, respiratory rate, oxygen saturation as well as cough relief persisted for ≥72 h.	HR: 1.75, 95 % CI: 1.10–2.79 Median time FPV: 3 days (95 % CI: 3–4 days) Control: 5 days (95 % CI: 4–6 days) RR: 1.02, 95 % CI: 0.94–1.12 FPV: 96.22 % SoC: 93.90 %		HR: 2.09, 95 % CI: 1.06–4.15 Median time FPV: 3.5 days (95 % CI: 3–4 days) Control: 6 days (95 % CI: 4–12 days) RR: 1.09, 95 % CI: 0.92–1.30 FPV: 95.83 % SoC: 87.50 %
Unfavorable for favipiravir (FPV)				
AlQahtani, 2022[37]	The proportion of patients who recovered based on a clinical scale <2 at the end of the study (hospital discharge)	RR: 1.03, 95 % CI: 0.86–1.23 FPV: 83.33 % SoC: 80.77 %		

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Table 2 (*continued*)

Reference	Parameters	Results		
		Overall	Mild	Moderate
Bosaeed, 2021[30]	Time to clinical recovery: normalization of temperature and respiratory symptoms, as well as the suppression of the cough, persisted for at least 72 h.	–	HR: 0.89, 95 % CI: 0.64–1.25 Median time FPV: 7 days (IQR: 4–11 days) Placebo + SoC: 7 days (IQR: 5–10 days)	–
Chuah, 2022[45]	Rate of clinical progression from nonhypoxia to hypoxia	RR:1.24, 95 % CI: 0.84–1.85 FPV: 18.40 % SoC: 14.80 %	RR: 1.38, 95 % CI: 0.71–2.67 FPV: 14.84 % SoC: 10.74 %	RR: 1.01, 95 % CI: 0.60–1.70 FPV: 18.85 % SoC: 18.60 %
Golan, 2022[43]	Time to sustained clinical recovery: based on oxygen saturation, oral temperature, and all COVID-19-associated symptoms for four consecutive days	Median time FPV: 7 days (95 % CI: 7–8 days) Control: 7 days (95 % CI: 6–8 days) Proportion: RR:1.01, 95 % CI: 0.96–1.05 F: 87.8 % SoC: 87.3 %		
Holubar, 2021[31]	Time to sustained symptom resolution: first of two consecutive days without symptoms.		HR: 0.87, 95 % CI: 0.52–1.45 Median time FPV: NA (95%CI: 26, NA) Placebo + SoC: 24 days (95%CI: 21, NA)	
Lou, 2021[41]	Time to an improvement of two points on a seven category the National Early Warning Score 2 (NEWS2) or live discharge from the hospital, whichever came first.			Median time FPV: 14 days (IQR: 6–38 days) Control: 15 days (IQR: 6–24 days) RR: 1.11, 95 % CI: 0.47–2.60 FPV: 55.55 % SoC: 50.00 %
McMahon, 2022[47]	Time to virological cure (two successive swabs negative for SARS-CoV-2 by PCR) Time to symptom resolution (fever, cough, sore throat, fatigue)	Time to virological cure: Log-rank p = 0.6 Fever: Log-rank p = 0.3 Cough: Log-rank p = 0.6 Sore throat: Log-rank p = 0.7 Fatigue: Log-rank p = 0.4		
Ruzhentsova, 2021[32]	Time to a reduction of patient clinical status on at least 1 score according to the WHO 8-Category Ordinal Scale compared to baseline.		HR: 1.60, 95 % CI: 0.78–3.26	
Shenoy, 2021[46]	Time to resolution of hypoxia: attainment of a score of four or lower on the WHO 10-point ordinal scale of clinical status			HR: 1.21, 95 % CI: 0.85–1.73 Median time FPV: 6 days Placebo: 7 days
Udwadia, 2021[34]	Time to clinical cure: according to clinician assessment and clinical parameters such as normalization of fever, respiratory rate, oxygen saturation as well as cough relief persisted for ≥72 h.		HR: 1.47, 95 % CI: 0.77–2.81 Median time FPV: 3 days (IQR: 2–4 days) Control: 4 days (IQR: 3–5 days) RR: 0.97, 95 % CI: 0.90–1.03 FPV: 96.55 % SoC: 100 %	

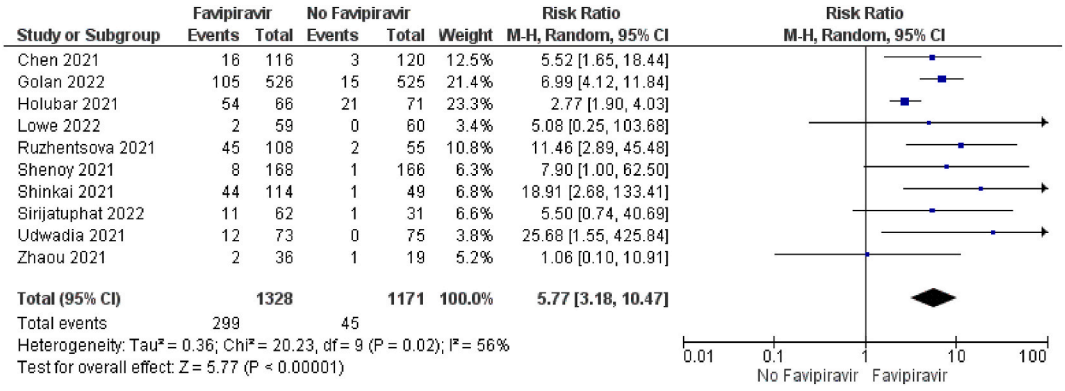

Fig. 5. The risk of hyperuricemia is higher in patients treated with favipiravir.

2.2. Search strategy

Papers reporting the results of randomized controlled trials published until January 6th, 2023, from PubMed, Embase, Web of Science, and Cochrane databases were systematically reviewed. The search queries for each database were developed by MAB with suggestions from DC and final checked by IYK, MM, and RB. The search strategy consists of two main keywords, "COVID-19" and "favipiravir". First, we built a systematic search strategy for the PubMed database by combining the keywords with medical subject headings [Mesh] terms, synonyms, and Boolean operators (AND, OR). The final query was then adjusted to the search strategy needed for other databases. We also did reference tracking from eligible articles and published systematic reviews and meta-analyses on favipiravir. Only full text artciles were considered. We applied no language restriction. The search results from all databases were sent to Rayyan (http://rayyan.qcri.org) to remove duplicate records and help the screening process. The complete search queries are available in the Supplementary material.

2.3. Record screening

The titles and abstracts of selected papers from each database were first screened by two independent reviewers (MAB and IYK). To reach a consensus, the conflicting screening results were discussed and the opinion of a third reviewer (DC) was sought. MAB and IYK then again screened the results by evaluating the full text independently to obtain the eligible studies. The disagreements were discussed, and the third reviewer's opinion was again asked to solve the discrepancies. We provide the level of inter-rater agreement for each step of the screening process using a percentage of agreement and Cohen's kappa (κ) statistic.

2.4. Data extraction

MAB and IYK extracted data independently using a data extraction form that had been pre-piloted. Data on the study characteristics (authors, year, country, study design), patient characteristics (number, age, sex), disease severity (mild or moderate), setting of care (inpatient or outpatient), drug information of intervention and comparator (dose, route of administration, duration), onset of symptoms to randomization, and parameters of efficacy and safety were extracted.

2.5. Study risk of bias assessment

The Cochrane risk-of-bias tool for randomized trials was used to assess the methodological quality of the included studies [9]. The appraisal of study quality was done by MAB and IYK separately. Disagreements between the two reviewers were resolved by discussion and the participation of the third reviewer (DC) was considered if no consensus was reached.

2.6. Statistical analysis

Time-to-event endpoints were measured with a hazard ratio (HR) and dichotomous endpoints were measured with a risk ratio (RR), with the exception of mortality, where – due to the zero risks – Risk Difference (RD) was used instead. Lowe et al. did not report HR on viral clearance but presented data (in its Supplementary Fig. 4) that made it possible to directly calculate HR under the assumption that patients who once had undetectable viral load will remain undetectable [10]. We provided a sensitivity analysis without the study by Lowe et al. in the Supplementary material (Fig. S1). All results are accompanied by a 95 % confidence interval (CI). A random-effects meta-analysis was used for the data analysis. The I^2 statistics and the standard χ^2 test were used to measure and detect statistical heterogeneity, respectively. The $I^2 > 50$ % and $p < 0.1$ indicated the presence of important heterogeneity [11]. Subgroup analyses were performed to identify the source of heterogeneity. Stratification based on the severity of the disease (mild/moderate) and the care

setting (inpatient/outpatient) on the primary outcome was performed in the subgroup analysis. Furthermore, a sensitivity analysis was also performed by excluding a study responsible for the statistical heterogeneity. A funnel plot and Egger's regression test were provided to detect publication bias for each main outcome. The Review Manager (RevMan) 5.4.1 software from Cochrane was used in this meta-analysis.

3. Results

3.1. Study selection

The systematic searching queries generated 883, 3334, 984, and 172 hits in PubMed, Embase, Web of Science, and Cochrane Library, respectively. After eliminating duplicate records (n = 1551), 3822 distinct entries were available for title and abstract (TIAB) screening. This first screening stage resulted in 49 eligible records that then entered the second stage of the screening process. The full-text assessment led to the exclusion of 29 articles for several reasons, such as retracted articles (n = 2), wrong study designs (n = 14), abstract proceeding (n = 3), favipiravir combined with another antiviral drug (n = 5), wrong comparison (n = 1), wrong severity (n = 3), and a parenteral administration (n = 1). Therefore, the final number of articles included was 20 (Fig. 1). For the TIAB screening, there was 99.5 % agreement between reviewers, with a kappa value of 0.71 (good). Meanwhile, the agreement rate for the entire text screening was 96.4 %, with a kappa value of 0.93 (very good).

3.2. Study characteristics

Among 20 articles, there were twelve open-label, seven double-blind, and one single-blind randomized controlled trial with mild to moderate COVID-19 severity. The location of the studies is quite diverse; there were four studies in Russia, three studies in China, and one study in Australia, Bahrain, Bangladesh, India, Iran, Japan, Kuwait, Malaysia, Saudi Arabia, Thailand, the UK, and the USA, respectively. There was one study that involved multiple countries, ie, Brazil, Mexico, and the USA. Based on the setting of patient care, there were 13 studies involving patients with inpatient care, five studies with patients attending outpatient care, and two with both types of patients. All studies used a loading dose of oral favipiravir on the first day of treatment with a range of doses between 1600, 1800 or 2200 mg two to three times a day. The dose of favipiravir on the second day of treatment until the end of the study (5–14 days) ranged from 1200 to 1800 mg daily, divided into two, three, or four doses. The duration from the onset of symptoms to the day of randomization was less than 12 days for most of the studies. The characteristics of each eligible article are presented in Table 1. Each study contains a variety of outcomes which are summarized in Supplementary material (Table S1).

3.3. Methodological assessments of articles

Of the 20 eligible articles, three studies did not provide detailed information on the randomization method and four did not mention whether the allocation of treatment to patients was concealed. Furthermore, there were twelve unblinded studies. The summary and graph of risk of bias can be found in Fig. 2 and Fig. S2, respectively.

3.4. Outcomes of meta-analysis

3.4.1. Primary efficacy outcomes

There were eight studies that reported the HR for viral clearence [10,12–18] (Supplementary material, Table S1). There were no statistically significant differences between the favipiravir and comparator groups in viral clearance (HR = 1.20 [95 % CI: 0.98–1.47, p = 0.09], I^2 = 40 %) (Fig. 3). The subgroup analysis by disease severity showed that favipiravir treatment significantly increased viral clearance by 59 % (HR = 1.59 [95 % CI: 1.25–2.03, p < 0.01], I^2 = 0 %) compared ot he comparators in patients with moderate severity of COVID-19 (Fig. 4). On the contrary, favipiravir had no significant effects on viral clearance (HR = 0.98 [95 % CI: 0.80–1.20, p = 0.85], I^2 = 0 %) in COVID-19 patients with mild symptoms (Fig. 4).

The results of subgroup analysis by healthcare settings indicated that the favipiravir group had significantly higher viral clearance (HR = 1.42 [95 % CI: 1.11–1.82, p < 0.01], I^2 = 20 %) in the inpatient care setting than in the comparator groups (Fig. S3). However, in the outpatient care setting, the comparable results for the viral clearance (HR = 1.01 [95 % CI: 0.77–1.33, p = 0.93], I^2 = 36 %) showed no significant effect of favipiravir (Fig. S3).

These results are also supported by the analysis of the proportion of patients who achieved viral clearance rather than the time to viral clearance. There were 13 studies that contained information on RR for viral clearance [10,12,13,15–17,19–25] (Table S1). Viral clearance was significantly higher in the groups treated with favipiravir with moderate severity (RR = 1.16 [95 % CI: 1.02–1.32, p < 0.01], I^2 = 0 %) and in those who were treated in the hospital (RR = 1.17 [95 % CI: 1.06–1.28, p < 0.01], I^2 = 18.9 %) than in the case of the comparators (Fig. S4a and Fig. S5a). This efficacy was not observed in the group treated with favipiravir with mild COVID-19 (RR = 1.01 [95 % CI: 0.95–1.07, p = 0.84], I^2 = 41.9 %) and in those who were treated in ambulatory care (RR = 1.04 [95 % CI: 0.92–1.17, p = 0.51], I^2 = 26.7 %) compared to the comparator groups (Fig. S4b and Fig. S5b).

3.4.2. Secondary efficacy outcomes

There were 16 studies that reported clinical improvement as an indicator to demonstrate the effectiveness of favipiravir. However, those studies used various parameters to define clinical improvements (Table 2). Seven studies indicated that favipiravir significantly

increased the likelihood of clinical recovery compared to the comparators. Among these studies, five studies demonstrated that favipiravir increased clinical cure in patients with COVID-19 with moderate symptoms significantly compared to the comparator groups [3,15,16,21]. There was only one study indicating that favipiravir significantly improved the clinical condition of COVID-19 patients with mild symptoms compared to the control group [18]. Another study did not have a subgroup analysis by severity [14,26].

Ten studies did not support that favipiravir was associated with a better clinical improvement than the comparators. Five studies provided evidence for patients with mild symptoms and three studies for patients with moderate symptoms [12,13,16,23,27,28]. There studies did not provide a subgroup analysis by severity [19,25,29].

All studies reported at least one of the other secondary outcomes that can be pooled in the meta-analysis (Table S1). The use of favipiravir was associated with a greater improvement in chest imaging (RR = 1.23 [95 % CI: 1.03–1.45, p = 0.02], I^2 = 20 %) than in the comparator group (Fig. S6a). There were no significant differences between the two groups for other outcomes such as mortality (RD = −0.00 [95 % CI: 0.01-0.00, p = 0.88], I^2 = 0 %), emergency department visits (RR = 1.15 [95 % CI: 0.50–2.66, p = 0.74], I^2 = 28 %), hospitalisations (RR = 1.05 [95 % CI: 0.54–2.05, p = 0.89], I^2 = 35 %), ICU (RR = 1.24 [95 % CI: 0.67–2.32, p = 0.49], I^2 = 0 %), and hospital discharge (RR = 1.09 [95 % CI: 0.96–1.24, p = 0.20], I^2 = 76 %) (Figs. S6b–g). The result for hospital discharge had substantial heterogeneity. Therefore, we performed a sensitivity analysis excluding one study, which decreased heterogeneity; however, the difference was still not significant (RR = 1.04 [95 % CI 0.97–1.12, p = 0.23], I^2 = 14 %) (Fig. S6g).

3.4.3. Safety outcomes

17 studies reported at least one side effect that can be analysed in the meta-analysis [3,10,12–20,23–26,28,29] (Table S1). The risks of developing low haemoglobin, hyperglycemia, elevated ALT and AST, high bilirubin, elevated creatine phosphokinase, high triglycerides, and leukopenia were comparable between the favipiravir and comparator groups (Fig. S7). Furthermore, the risks that both groups would experience other symptoms, such as abdominal pain, anorexia, constipation, diarrhea, dizziness, dyspnea, headache, myalgia, nasal congestion, nausea, rhinorrhoea, skin rash and vomiting, were also not significantly different (Fig. S8). It is noteworthy that the frequency of these symptoms might be influenced by the disease itself. However, a meta-analysis of ten studies indicated that patients treated with favipiravir were almost six times more likely to develop hyperuricemia than those who did not receive favipiravir (RR = 5.77 [95 % CI 3.18–10.47, p < 0.01], I^2 = 56 %) (Fig. 5) [3,10,13–18,25,28]. Since heterogeneity was moderate, we performed a sensitivity analysis excluding a study by Holubar et al. (2021) [13]. The result indicated that the favipiravir regimen increased the risk of hyperuricemia more than seven times (RR = 7.12 [95 % CI: 4.73–10.72, p < 0.01], I^2 = 0 %) compared to the comparator treatment. (Fig. S9). In general, favipiravir can be considered a safe drug since the incidence of adverse events observed in the favipiravir group was not significantly different from the comparator group, except for the risk of hyperuricemia.

3.5. Publication bias

The funnel plots for the primary outcome (viral clearance) and the safety outcome (hyperuricemia) were presented in the Supplementary material (Figs. S10a–b). The Egger's regression test results (p > 0.05) indicated no publication bias for the outcomes. However, the Cochrane handbook recommended not to use the funnel plot and Egger's regression test if the number of studies included in the meta-analysis of the outcomes is less than ten studies since the test would have a low power to detect the real asymmetry [9]. In our analysis, the number of included studies for viral clarance is below ten.

4. Discussion

Favipiravir has been used in many countries to treat COVID-19 infections shortly after the outbreak of the pandemic [5,6]. Although this was an off-label application, the lack of drugs with proven efficacy required the use of repurposed drugs, the efficacy of which could be based mainly on preclinical data. The efficacy of favipiravir has been studied in several clinical trials since its introduction into COVID-19 therapy [3,4]. The results of these trials have been summarized in meta-analyses. The findings of these meta-analyses do not allow a definitive conclusion to be drawn on the efficacy of favipiravir. This could be attributable in part to the diversity of study populations, interventions, comparators, and results. The first meta-analysis was published in September 2020. Altogether, four studies were included in the quantitative synthesis, one of which was not randomized. There was a statistically significant clinical improvement in the favipiravir group on day 14 compared to other antivirals or standard of care (RR = 1.29, 95 % CI 1.08–1.54). No significant differences were observed between the two groups in non-invasive ventilation or oxygen requirement (OR = 0.76, 95 % CI: 0.42–1.39), viral clearance (day 14: RR = 1.06, 95 % CI: 0.84–1.33), and adverse effects (OR = 0.69, 95 % CI: 0.13–3.57) [30].

The most recent meta-analysis evaluated the efficacy and adverse effects of favipiravir based on randomized clinical trials, observational studies, case series, and case reports. Overall, 157 studies (the majority of which were case reports) were included. Favipiravir showed a higher rate of viral clearance on day 5 (RR = 1.60, p = 0.02) in hospitalized patients compared to standard of care. A similar finding was made for chest radiological improvement (RR = 1.33, p < 0.01), normalization of body temperature on days 3–4 (RR = 1.99, p < 0.01), hospital discharge on days 10–11 (RR = 1.19, p < 0.01), and shorter clinical improvement time (MD = −1.18, p = 0.05). In patients treated with favipiravir, the risk of hyperuricemia was higher (RR = 9.42, p < 0.01), as was the increase in alanine aminotransferase (RR = 1.35, p < 0.01). There were no differences in the increase in aspartate aminotransferase level (RR = 1.11, p = 0.25). Nausea (RR = 0.42, p < 0.01) and vomiting (RR = 0.19, p = 0.02) was less frequent in the favipiravir group. There were no differences in mortality (RR = 1.19, p = 0.32). In the case of non-hospitalized patients, no significant differences were reported [31].

Our meta-analysis is the first meta-analysis of randomized controlled trials that assesses the efficacy of favipiravir in viral clearance time as the primary outcome measure. Since no significant differences in viral clearance rate (HR = 1.20 [95 % CI: 0.98–1.47, p = 0.09], $I^2 = 40$ %) could be detected compared to comparator treatment, the use of favipiravir as first choice treatment is questionable. Its beneficial effects could only be confirmed in patients with moderate symptoms (59 % significant increase in the rate of viral clearance (HR = 1.59 [95 % CI: 1.25–2.03, p < 0.01], $I^2 = 0$ %)), however, this finding does not support the use of favipiravir as routine therapy that should be started after the diagnosis of COVID-19. No beneficial effect was observed in those with mild symptoms. According to previous data, favipiravir significantly increased the risk of hyperuricemia (RR = 5.77 [95 % CI: 3.18–10.47, p < 0.01], $I^2 =$ 56 %) compared to the comparator group, which should be considered when making therapeutic decisions.

The main strength of our trial is that the meta-analysis is based only on the results of randomized, controlled trials. The 20 included trials were carried out by independent research groups in different countries in Europe, America, Asia, and Australia. However, our study has several limitations that require special caution when interpreting the results. Although the studies were randomized, many of them were open-label trials. Study populations may be heterogeneous in several aspects and the measure of heterogeneity is predominantly unknown due to inadequate reporting. First, the included trials were published between 2020 and 2022, when COVID-19 was caused by different variants of SARS-CoV-2; however, most of the trials did not include the identification of virus variants. Second, the grading of clinical severity (which has influence on hospitalization as well) may differ in different countries and hospitals, and the criteria by which grading was performed was not available in the studies. Third, standard-of-care therapies might be diverse geographically and in time - unfortunately, the exact therapeutic protocols were mostly not disclosed in the individual studies. Fourth, younger adults are over-represented in the majority of the trials; moreover, the exact age distribution could not be determined based on the available data. Fifth, although it is known that favipiravir is more effective in the first phase of the disease, in some trials randomization was performed within 10–12 days of the onset of initial symptoms. Sixth, the vaccination status of the patients was unclear. And finally, some applied methods (PCR analysis, temperature measurement) were not described in the studies, which may also be a source of heterogeneity. However, from the point of view of rational pharmacology, these limitations do not undermine the principal conclusion of our study, which is that the use of favipiravir in mild to moderate COVID-19 is not justified by available data.

5. Conclusions

Favipiravir treatment did not have a significant effect on the viral clearance rate compared to comparator treatment. Its efficacy could be demonstrated in a subgroup analysis of patients with moderate severity COVID-19, however, favipiravir had no significant effects on viral clearance in patients with COVID-19 with mild symptoms and treated in ambulatory care. Based on these results, the use of favipiravir as a routine therapy that should be initialized after the diagnosis of COVID-19 is questionable.

Ethics statement

Review and/or approval by an ethics committee was not needed for this study because as a systematic review article does not require ethical approval. Our systematic review and meta-analysis protocol was registered with PROSPERO (registration number CRD4202232443).

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Ethics declarations

Review and/or approval by an ethics committee was not needed for this study because this research is a meta-analysis of already publisjhed data.

Data availability statement

All the data that are the basis of this study can be found in the article or the supplementary material.

CRediT authorship contribution statement

Muh Akbar Bahar: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ikhwan Yuda Kusuma:** Writing – original draft, Methodology, Investigation, Formal analysis. **Ádám Visnyovszki:** Writing – review & editing. **Mária Matuz:** Writing – review & editing. **Ria Benkő:** Writing – review & editing. **Tamás Ferenci:** Writing – review & editing, Methodology. **Bálint Gergely Szabó:** Writing – review & editing. **Edit Hajdú:** Writing – review & editing. **Zoltán Pető:** Writing – review & editing. **Dezső Csupor:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used Writefull in order to improve language. After using this tool/service, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e29808.

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Telepharmacy in Indonesia: Navigating Knowledge, Perception, and Readiness Among 6,000 Pharmacists and Related Sociodemographic Determinants

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Abstract

Introduction: *Telepharmacy can improve the delivery of pharmaceutical care services to patients. However, there are limited data regarding the knowledge, perceptions, and readiness (KPR) for telepharmacy in Indonesia. In this cross-sectional survey study, we assessed KPR and associated factors among Indonesian pharmacists, aiming to implement telepharmacy services in the future.*

Methods: *Eligible participants were recruited from all provinces of Indonesia through a 24-item instrument. KPR scores were classified as low, moderate, and high. Sociodemographic characteristics and KPR of participants were summarized using descriptive statistics. Bivariate/multivariate ordinal logistic regression analyses were conducted to identify independent determinants of KPR. An adjusted odds ratio (AOR) with a 95% confidence interval (CI) was calculated for each determinant.*

Results: *A total of 6,059 pharmacists provided responses. Overall, 58.28% had a high knowledge score, and 63.51% expressed moderate perceptions toward telepharmacy services. Moreover, 70.21% showed a moderate level of readiness. Gender (male; AOR: 1.21 [95% CI: 1.06–1.39]), stable internet access (AOR: 0.75 [95% CI: 0.64–0.86]), and central region (AOR: 1.13 [95% CI: 0.99–1.29]) were significantly associated with perception toward telepharmacy. Readiness was significantly associated with age (17–25 years; AOR: 0.73 [95% CI: (0.60–0.89]), gender (male; AOR: 0.83 [95% CI: 0.72–0.95]), stable internet access (AOR: 0.75 [95% CI: 0.64–0.89]), education level (master/doctoral; AOR: 1.33 [95% CI: 1.06–1.67]), and central region (AOR: 1.29 [95% CI: 1.12–1.49]). Interestingly, knowledge levels were not significantly correlated with specific factors.*

Conclusions: *Participants demonstrated high knowledge, without significant influencing factors. However, they showed moderate perceptions and readiness levels, influenced by sociodemographic factors, including gender, age, education level, internet access, and regional disparities. Therefore, targeted interventions (e.g., telepharmacy training and regional outreach) are imperative to enhancing perceptions and readiness, fostering the effective integration of telepharmacy services, and advancing pharmaceutical care in Indonesia.*

Keywords: *knowledge, perception, pharmacists, readiness, telepharmacy, telemedicine*

Introduction

Telepharmacy falls under the umbrella of telemedicine and strongly influences the provision of pharmaceutical services by pharmacists using information communication and technology tools.[1] This type of service has been recognized by several international organizations, including the World Health Organization,[2] which identified telepharmacy as a priority area for the development of telemedicine.[1,3] As a virtual approach, telepharmacy has provided significant benefits to patients and the health care sector (e.g., improvement in access to health care services and medicines, improvement in real-time diagnoses and treatments, seamless real-time communication, and the creation of a large-scale cyber health care system).

In addition, telepharmacy can facilitate the provision of a wide range of pharmaceutical services in remote/deprived areas where access to health care care is limited due to economic or geographical challenges.[4,5] However, disadvantages have also been reported, such as decreased human interaction between health professionals and patients, data security threats, and low acceptance within the health care sector.[4,5] At present, telepharmacy is rarely used by pharmacists for managing diseases, although its use was more widespread during the coronavirus disease-2019 pandemic.[6,7]

The implementation of telepharmacy has been growing rapidly in recent years, particularly in developed countries, such as the United States (U.S.) and European countries. In these countries, telepharmacy has been embraced, particularly during the pandemic.[7,8] Nevertheless, there is a limited number of studies focusing on the knowledge, perception, and readiness (KPR) related to the implementation of telepharmacy in developing countries, such as Malaysia,[9] Nigeria,[10] Vietnam,[11] Philippines,[12] and Indonesia.[13] In Indonesia, telepharmacy services are not formally accepted as a pharmaceutical service; hence, this type of service is not widely implemented.

Sociodemographic factors can significantly influence the adoption and implementation of telepharmacy practices. Thus, it is important to investigate the association between factors and KPR for telepharmacy. The professional education level, age, and work experience of pharmacists can influence their knowledge, attitude, and practice with regard to the delivery of care.[14] These factors may also influence their knowledge, attitude, and practice toward telepharmacy. Recent studies have shown that junior community pharmacists and those with higher educational levels and experience using technology tend to have more positive attitudes toward telepharmacy.[15] This aligns with previous research indicating that younger pharmacists and pharmacy students have a better understanding of health information technologies, likely due to their greater exposure to and use of technology.[16–18]

Indonesia is the largest archipelago globally and the most populous nation in Southeast Asia, comprising 17,508 islands and 34 provinces with a population exceeding 260 million. The country faces challenges in providing adequate health care access, particularly in rural and remote areas. For example, there is limited access to health care facilities, including pharmacies, in numerous regions of the country.[19] Telepharmacy offers a promising solution to this problem, as it enables pharmacists to provide remote pharmaceutical care to patients residing in these underdeveloped areas[1,20] and reduce health inequalities.[1,21] Pharmacists play a crucial role in pharmaceutical services, and their KPR toward telepharmacy significantly influences the successful implementation of telepharmacy services.[6] The KPR of pharmacists toward telepharmacy and associated factors can be used by health care organizations, policymakers, and telepharmacy service providers to design specific interventions that can aid in the successful implementation of telepharmacy services.

The aim of this study was to investigate the level of KPR for telepharmacy and associated sociodemographic factors among Indonesian pharmacists.

Methods

STUDY DESIGN AND PARTICIPANTS

A cross-sectional study was conducted across all 34 provinces of Indonesia. We used the online survey platform to collect the data from August 1, 2022, to August 7, 2022. All registered pharmacists practicing in Indonesia and willing to voluntarily participate in the study were considered eligible.

INSTRUMENTS

In this study, a 24-item instrument was used to investigate KPR for telepharmacy and sociodemographic determinants. Participants were asked to respond to questions regarding their personal background (i.e., age, gender, work experience, education level, and residence) and KPR for telepharmacy.

The KPR for telepharmacy questionnaire, developed by Kusuma et al. (Supplementary Appendix S1–S4), was used.[22] Knowledge was assessed using eight items (Cronbach's alpha = 0.961) (Supplementary Appendix S5). For instance, statements included "Telepharmacy requires a strong internet connection or high-performance technology" and "Telepharmacy provides better counseling in terms of privacy and the length of the session." Responses

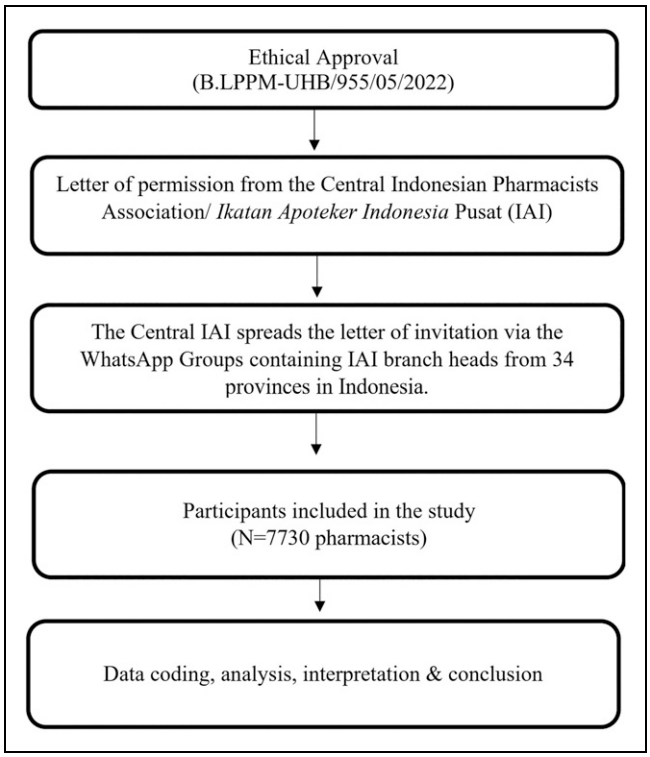

Fig. 1. Study flow diagram. IAI = Ikatan Apoteker Indonesia Pusat (Central Indonesian Pharmacists Association). *N* = number of respondents.

to those statements included "*yes*" and "*no*," with a score of 1 and 0 assigned to each correct and incorrect answer, respectively. Perception was evaluated with eight items (Cronbach's alpha = 0.959) (Supplementary Appendix S5). For example, questions included: "Do you think telepharmacy will improve the patient's adherence to the medication?" and "Do you feel telepharmacy will enhance the patient's access to health care services?" Readiness was measured with eight items (Cronbach's alpha = 0.963) (Supplementary Appendix S5). For example, statements included: "I am ready to work on telepharmacy projects even in rural areas without an incentive" and "I am ready to conduct drug counseling via two-way video consultation, such as a telephone call, text message, or voice call through mobile applications." Both perception and readiness were rated using a 5-point Likert scale (1 = *strongly disagree*, 2 = *disagree*, 3 = *neutral*, 4 = *agree*, and 5 = *strongly agree)*. The knowledge, attitude, and perception indices were converted to a scale ranging from 0% to 100% representing the worst and best possible scores, respectively. For knowledge, which involved dichotomous questions, the formula used was: (correct answer/total answer) × 100%. For perception and readiness, the total score from the Likert scale was calculated using the following formula: [(obtained score – lowest possible score)/(maximum possible score–minimum possible score)] × 100%.

In addition, we transformed Likert scale scores, ranging from 1 to 5, into a percentage scale with corresponding categories: 0–20% (Strongly disagree), 21–40% (Disagree), 41–60% (Neutral), 61–80% (Agree), and 81–100% (Strongly agree). For each domain, higher scores indicate higher KPR. The score for each domain was calculated based on the mean score of items within that domain.[23,24] Scores <50%, 50–70%, and >70% indicate low, moderate, and high levels of KPR, respectively.[25,26]

Table 1. Descriptive Characteristics of Study Participants (*n* = 6,059)

CHARACTERISTICS	NUMBER	%
Age	6,059	
17–25 years	832	13.73%
26–35 years	3,662	60.44%
36–45 years	1,241	20.48%
>45 years	324	5.35%
Gender		
Male	1,132	18.68%
Female	4,927	81.32%
Education level		
Pharmacist	5,690	93.91%
Master/doctoral	369	6.09%
Field of work		
Community pharmacy	3,217	53.09%
Hospital	1,470	24.26%
Public health center	1,372	22.64%
Internet access		
Stable	5,109	84.32%
Unstable/poor	950	15.68%
Residence		
Rural	2,068	34.13%
Urban	3,991	65.87%
Region		
West region	4,753	78.45%
Central region	1,102	18.19%
East region	204	3.37%

Table 2: Knowledge and Potential Determinants of Knowledge Toward Telepharmacy

	KNOWLEDGE ($N = 6,059$)							
VARIABLES	LOW	%	MODERATE	%	HIGH	%		
TOTAL STUDY POPULATION	9	0.15%	2,519	41.57%	3,531	58.28%	*p* VALUE	OR (CI 95%)
Age								
17–25 years	1	0.12%	331	39.78%	500	60.10%		Ref.
26–35 years	3	0.08%	1,555	42.46%	2,104	57.45%	**0.17**	0.90 (0.77–1.05)
36–45 years	3	0.24%	506	40.77%	732	58.98%	0.60	0.95 (0.80–1.14)
>45 years	2	0.62%	127	39.20%	195	60.19%	0.97	0.99 (0.77–1.29)
Gender								
Male	1	0.09%	480	42.40%	651	57.51%	0.58	0.96 (0.85–1.10)
Female	8	0.16%	2,039	41.38%	2,880	58.45%		Ref.
Education level								
Pharmacist	9	0.16%	2,350	41.29%	3,332	58.55%		Ref.
Master/ Doctoral	0	0.00%	169	45.92%	199	54.08%	**0.11**	0.84 (0.68–1.04)
Field of work								
Community pharmacy	8	0.25%	1,308	40.66%	1,901	59.09%		Ref.
Hospital	1	0.07%	634	43.13%	835	56.80%	0.16	0.91 (0.81–1.04)
Public health center	0	0.00%	577	42.06%	795	57.94%	0.51	0.96 (0.84–1.09)
Internet access								
Stable	7	0.14%	2,117	41.44%	2,984	58.42%		Ref.
Unstable/poor	2	0.21%	402	42.27%	547	57.52%	0.53	0.96 (0.83–1.10)
Residence								
Rural	3	0.15%	848	41.01%	1,217	58.85%	0.55	1.03 (0.93–1.15)
Urban	6	0.15%	1,671	41.87%	2,314	57.98%		Ref.
Region								
West region	6	0.13%	1,982	41.68%	2,767	58.19%		Ref.
Central region	2	0.18%	458	41.60%	641	58.22%	0.97	1.00 (0.87–1.14)
East region	1	0.49%	79	38.92%	123	60.59%	0.59	1.08 (0.81–1.44)

$p < 0.05$ indicates statistical significance.

CI, confidence interval; OR, odds ratio; Ref, reference.

ETHICAL APPROVAL

The present survey-based study was ethically approved by the Health Research Ethics Committee of Universitas Harapan Bangsa, Indonesia (approval number: B.LPPM-UHB/955/05/2022). Participants were informed regarding the study objective, procedures, and potential risks and benefits before providing consent for their participation. Informed consent was provided electronically. This research study was conducted in accordance with established ethical guidelines, ensuring the safety, confidentiality, and privacy of the participants.

PROCEDURES

Data collection involved several steps. First, we sent a request letter to the Central Indonesian Pharmacists Association

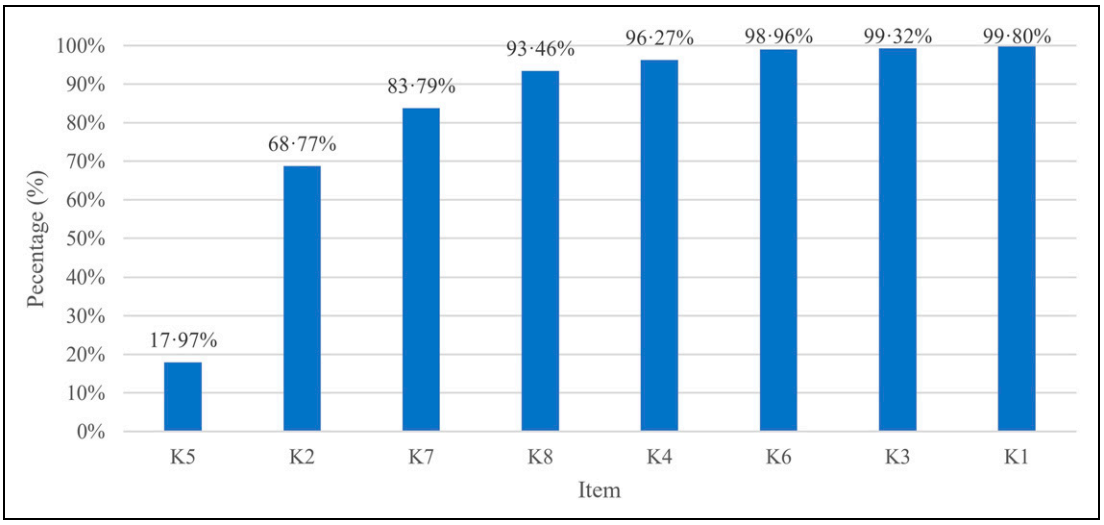

Fig. 2. Percentage of correct responses to questions concerning knowledge for telepharmacy.

(*Ikatan Apoteker Indonesia Pusat* [IAI]). Second, after obtaining permission, the Indonesian Pharmacists Association assisted in the data collection process. Third, the letter of invitation to participate in our survey was distributed to the branch heads of IAI groups in the 34 provinces in Indonesia through the WhatsApp application (Facebook, Inc.); the provinces were divided into three regions according to the time zone.

The researchers declared data confidentiality; only participants and researchers had access to raw data. The study flow diagram is presented in Fig. 1.

DATA ANALYSIS

All analyses were performed with the Statistical Package for Social Sciences Software (SPSS), version 26.0 (SPSS, IBM Corp., Armonk, NY). Descriptive statistics were used to analyze the sociodemographic characteristics of the participants. Categorical variables are presented as numbers and percentages, while continuous variables are presented as mean and standard deviation. Bivariate analysis was conducted to identify potential determinants between variables. Multivariate ordinal logistic regression analysis was performed to examine the independent relationships between sociodemographic variables and KPR toward telepharmacy. Potential factors that displayed a significant association with KPR (i.e., $p < 0.25$) in the bivariate analysis were included in the multivariate ordinal logistic regression analysis. The resulting odds ratios and 95% confidence intervals were derived, with $p < 0.05$ denoting statistical significance.

Results

SOCIODEMOGRAPHIC CHARACTERISTICS OF THE STUDY PARTICIPANTS

The sociodemographic characteristics of the participants are presented in Table 1. The study involved 6,059 pharmacists from health care facilities across the country.

More than half of the participants were aged between 26 and 35 years (n = 3,662, 60.44%). There was a predominance of female over male pharmacists (81.32% vs. 18.68%, respectively). The majority of the participants held a pharmacist's degree (n = 5,690, 93.91%), worked in community pharmacy (n = 3,217, 53.09%), had stable internet access (n = 5,109, 84.32%), resided in urban areas (n = 3,991, 65.87%), and were from the West Region of Indonesia (n = 4,753, 78.45%).

FACTORS ASSOCIATED WITH KPR

Of the respondents, 58.28% had a high knowledge level regarding telepharmacy, and only 0.15% of participants had a low level of knowledge (Table 2). Our data showed that 99.80% of participants responded correctly to K1 "Telepharmacy is the provision of pharmaceutical care at a distance through information and communication technology by pharmacists," as shown in Fig. 2. The lowest rate of correct answers (17.97%) was observed for K5 "Counseling via telepharmacy is more expensive."

Approximately one-third of the participants (34.96%) had high scores regarding perception. Notably, 1.53% and 63.51% of patients exhibited low and moderate levels of perception, respectively (Table 3). Our results indicate that the highest percentage score on perception was achieved on P5

Table 3: Bivariate Analysis of Perception and Potential Determinants of Perception Toward Telepharmacy

	PERCEPTION ($N = 6,059$)							
VARIABLES	Low	%	MODERATE	%	HIGH	%		
TOTAL STUDY POPULATION	93	1.53%	3,848	63.51%	2,118	34.96%	*p* VALUE	OR (CI 95%)
Age								
17–25 years	11	1.32%	540	64.90%	281	33.77%		Ref.
26–35 years	58	1.58%	2,320	63.35%	1,284	35.06%	0.55	1.05 (0.90–1.23)
36–45 years	18	1.45%	803	64.71%	420	33.84%	0.99	1.00 (0.83–1.20)
>45 years	6	1.85%	185	57.10%	133	41.05%	**0.03**	1.33 (1.03–1.73)
Gender								
Male	18	1.59%	675	59.63%	439	38.78%	**<0.01**	1.21 (1.06–1.39)
Female	75	1.52%	3,173	64.40%	1,679	34.08%		Ref.
Education level								
Pharmacist	90	1.58%	3,625	63.71%	1,975	34.71%		Ref.
Master/ Doctoral	3	0.81%	223	60.43%	143	38.75%	**0.09**	1.21 (0.97–1.49)
Field of work								
Community Pharmacy	59	1.83%	2,017	62.70%	1,141	35.47%		Ref.
Hospital	19	1.29%	921	62.65%	530	36.05%	0.54	1.04 (0.92–1.18)
Public health center	15	1.09%	910	66.33%	447	32.58%	**0.13**	0.90 (0.79–1.03)
Internet access								
Stable	72	1.41%	3,201	62.65%	1,836	35.94%		Ref.
Unstable/Poor	21	2.21%	647	68.11%	282	29.68%	**<0.01**	0.75 (0.64–0.86)
Residence								
Rural	40	1.93%	1,359	65.72%	669	32.35%	**<0.01**	0.83 (0.74–0.93)
Urban	53	1.33%	2,489	62.37%	1,449	36.31%		Ref.
Region								
West region	73	1.54%	3,038	63.92%	1,642	34.55%		Ref.
Central region	18	1.63%	670	60.80%	414	37.57%	**0.07**	1.13 (0.99–1.29)
East region	2	0.98%	140	68.63%	62	30.39%	0.28	0.85 (0.63–1.14)

$p < 0.05$ indicates statistical significance.

CI, confidence interval; OR, odds ratio; Ref, reference.

(86.16%); the participants strongly agreed that pharmacy schools should provide education programs encompassing topics on computational skills, information technology, and telepharmacy to assist in the future utilization of telepharmacy. However, the lowest score (72.43%) was recorded for P4 "Do you think therapy monitoring by telepharmacy would be cost-effective compared to a direct consultation at a pharmacy?" (Fig. 3).

As shown in Table 4, 24.34%, 70.21%, and 5.45% of participants demonstrated a high, moderate, and low level of readiness, respectively. According to Fig. 4, the highest percentage score on readiness was obtained for item R4. The majority of participants (80.78%) strongly agreed that they are willing to undergo training in ethics and legal issues related to telepharmacy. In contrast, the lowest score

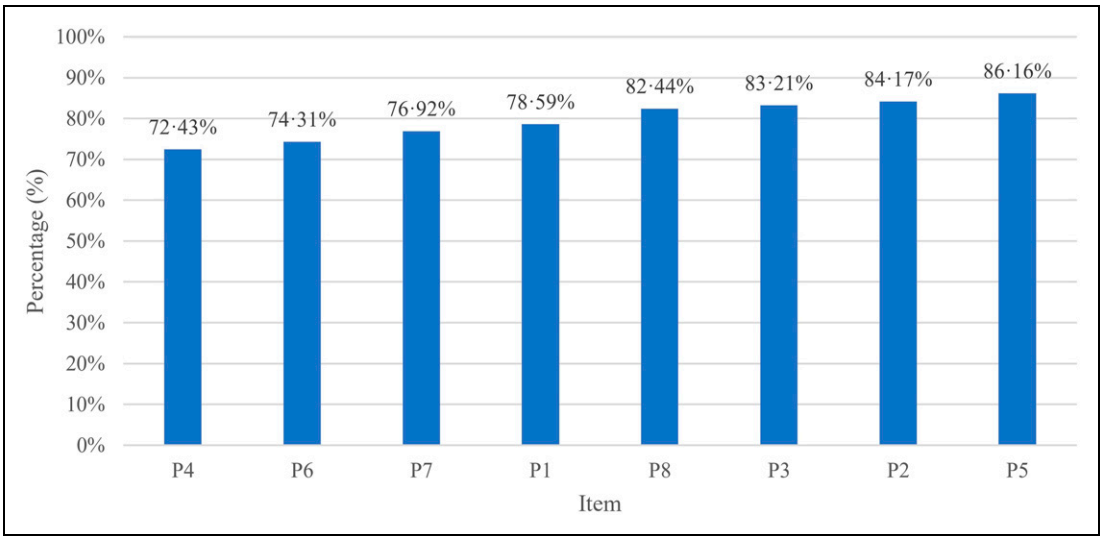

Fig. 3. Percentage of "Strongly agree" responses to questions regarding perception of telepharmacy.

(54.93%) was obtained for R1 "I am ready to work on telepharmacy projects even in rural areas without an incentive."

Regarding sociodemographic determinants, age, gender, education level, internet access, residence, and region demonstrated $p < 0.25$ in the bivariate analysis. Thus, these factors were included into the multivariate ordinal logistic regression model.

The results of the multivariate ordinal regression revealed that gender, internet access, and region had significant associations with higher perception and readiness scores ($p < 0.05$). Furthermore, age and education level were significantly associated with readiness. Interestingly, the factors were not significantly correlated with knowledge levels regarding telepharmacy (Table 5).

Discussion

To the best of our knowledge, this is the first study performed in Indonesia to assess the KPR toward telepharmacy and potential sociodemographic determinants.

Our results indicated that more than half (58.28%) of respondents had a high knowledge level. This is similar to a study conducted in Malaysia, in which 67% of the participants had a high level of knowledge.[9] In addition, 99.32% of the current study respondents agreed that telepharmacy requires a strong internet connection or high-performance technology. This is different from the results of a previous study carried out in Saudi Arabia, in which only 40.61% of the participants agreed that telepharmacy requires a strong internet connection or high-performance technology.[27] This variance might be due to differences in the study population and the time of the study. It has been reported that the success of telepharmacy services depends largely on the level of technological infrastructure, such as efficient Internet connection.[1]

Pharmacists are in charge of providing pharmaceutical care to patients, who may not have direct contact with them (i.e., through telecommunication).[4] Almost all participants in the present study agreed that pharmacists play an important role in telepharmacy services.

Furthermore, 96.27% of the participants agreed that telepharmacy provides better counseling than traditional pharmacy practice in terms of privacy and the duration of the session. This is consistent with the findings of a study conducted in the United States on telepharmacy-related services. Pharmacists recommended using webcam-enabled telepharmacy services, as it enabled them to provide better privacy and longer counseling sessions compared with traditional pharmacy practice.[28]

Moreover, the majority of our study respondents stated that telepharmacy services could be conducted using electronic technology tools, such as video conferencing. The use of telepharmacy was particularly promoted during the recent pandemic, to facilitate the provision of instructions on the use of medication and teach back.[29–31] However, a cross-sectional study from the Netherlands revealed very limited use of video communication for the provision of pharmaceutical care services via telepharmacy during the pandemic.[32]

Surprisingly, only 17.97% of our study participants agreed that counseling via telepharmacy is less expensive compared with traditional pharmacy services. This is contradictory to previously published evidence indicating that telepharmacy is beneficial in terms of conserving resources.[3] Strikingly different from our findings, 91% of participants in a study conducted in Malaysia considered that employing a telepharmacy system might save time and be a cost-effective option for patients.[9] The above difference may be explained by the lack of

Table 4: Bivariate Analysis of Readiness and Potential Determinants of Readiness Toward Telepharmacy

	READINESS ($N = 6,059$)							
VARIABLES	LOW	%	MODERATE	%	HIGH	%		
TOTAL STUDY POPULATION	330	5.45%	4,254	70.21%	1,475	24.34%	*p* VALUE	OR (CI 95%)
Age								
17–25 years	34	1.29%	579	22.00%	219	26.32%		Ref.
26–35 years	200	5.46%	2,559	69.88%	903	24.66%	**0.14**	0.89 (0.76–1.04)
36–45 years	77	6.20%	903	72.76%	261	21.03%	**<0.01**	0.73 (0.61–0.89)
>45 years	19	5.86%	213	65.74%	92	28.40%	0.83	1.03 (0.78–1.36)
Gender								
Male	64	5.65%	751	66.34%	317	28.00%	**0.01**	1.21 (1.05–1.39)
Female	266	5.40%	3,503	71.10%	1,158	23.50%		Ref.
Education level								
Pharmacist	316	5.55%	4,008	70.44%	1,366	24.01%		Ref.
Master/ Doctoral	14	3.79%	246	66.67%	109	29.54%	**0.01**	1.35 (1.08–1.68)
Field of work								
Community Pharmacy	199	6.19%	2,235	69.47%	783	24.34%		Ref.
Hospital	61	4.15%	1,035	70.41%	374	25.44%	**0.08**	1.13 (0.99–1.29)
Public Health Center	70	5.10%	984	71.72%	318	23.18%	0.86	0.99 (0.86–1.13)
Internet access								
Stable	264	5.17%	3,568	69.84%	1,277	25.00%		Ref.
Unstable/Poor	66	6.95%	686	72.21%	198	20.84%	**<0.01**	0.78 (0.67–0.91)
Residence								
Rural	131	6.33%	1,450	70.12%	487	23.55%	**0.08**	0.90 (0.80–1.01)
Urban	199	4.99%	2,804	70.26%	988	24.76%		Ref.
Region								
West region	271	5.70%	3,379	71.09%	1,103	23.21%		Ref.
Central region	50	4.54%	742	67.33%	310	28.13%	**<0.01**	1.29 (1.12–1.49)
East Region	9	4.41%	133	65.20%	62	30.39%	**0.02**	1.43 (1.06–1.91)

$p < 0.05$ indicates statistical significance.

CI, confidence interval; OR, odds ratio; Ref, reference.

telepharmacy implementation in Indonesia, which limits the awareness of pharmacists regarding certain telepharmacy-related aspects. Moreover, counseling services in traditional pharmacies remain free of charge in Indonesia, especially for patients covered by national health insurance. The provision of an online counseling service via telepharmacy requires costs for infrastructure (i.e., electronic devices and Internet fees).

The majority of participants reported a positive perception of telepharmacy. This finding is comparable to those of studies conducted in Malaysia[9] and Jordan.[6] However, it is inconsistent with the results of a study conducted in Pakistan, in which 59.7% of the pharmacists had a negative perception toward the implementation of telepharmacy.[33] This difference may be attributed to different methods utilized

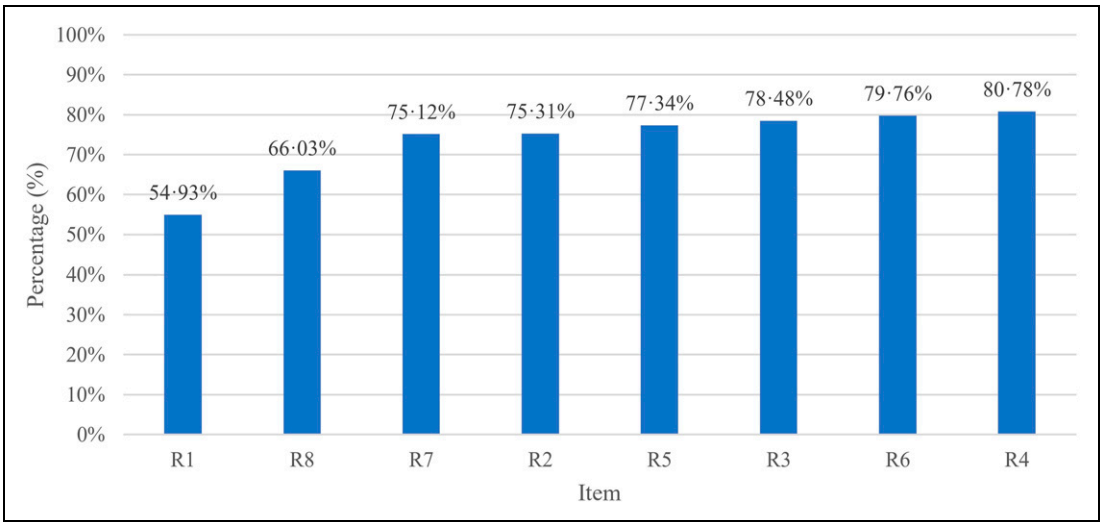

Fig. 4. Percentage of "Strongly agree" responses to questions concerning readiness toward telepharmacy.

for the evaluation of perception. In the present study, 86.16% of the participants strongly agreed that pharmacy schools should provide education programs on computers, information technology, and telepharmacy to assist in the future utilization of telepharmacy. This concept was supported by other studies promoting the importance of information technology knowledge for pharmacy students to provide them with the necessary skills for future professional practice.[1,9,34]

Most participants agreed that telepharmacy would improve access to health care services for patients, as well as increase the effectiveness of patient consultation. This is consistent with data from other studies showing that an improvement in access to medication and information in rural areas through telepharmacy eliminates prominent barriers, such as costs and travel time. Consequently, these effects increase the trust and satisfaction of patients with regard to telepharmacy services.[1,21] Moreover, 78.59% of pharmacists agreed that telepharmacy would improve adherence to medication among patients compared with traditional pharmacy services. Other studies reported significant improvement in adherence through telepharmacy services.[35,36]

Our study participants were skeptical concerning the possibility that therapy monitoring through telepharmacy would be a cost-effective option compared with face-to-face consultation. Nevertheless, this finding could be attributed to the lack of previous experience in telepharmacy services among Indonesian pharmacists, as well as the coverage of costs by the national health insurance scheme. A study conducted by the U.S. Department of Veterans Affairs integrated a health care system for patients who required anticoagulation management services in a community outpatient clinic. The results showed that the rate of achievement of the international therapeutic normalized ratio remained stable between previous face-to-face management and clinical video telehealth, with higher levels of patient satisfaction observed with the latter approach.[37]

In addition, 94.55% of the participants had a moderate-to-high level of readiness. This result is higher than those of a previous study conducted in Malaysia, in which the rate of readiness toward telepharmacy was 68%.[9] Another study conducted in Saudi Arabia reported a lower rate (<40%) of telepharmacy readiness among participants. These observations may be explained by the limited availability of telepharmacy in Malaysia and Saudi Arabia, which introduces skepticism and uncertainty regarding the adoption of this approach.[27] Most of our study participants agreed to undertake all activities and training relevant to telepharmacy practice. However, they expressed concern regarding the lack of incentive for extended telepharmacy services. Furthermore, participants were concerned regarding the potential increment in their workload when providing telepharmacy services. Other studies reported that the workload, lack of an incentive, and reimbursement are significant barriers to telepharmacy practice.[1,9,38] Therefore, a balanced workload and reimbursement for the service providers should be carefully considered for the development of a sustainable telepharmacy program.

Numerous sociodemographic factors were identified as predictors of perception and readiness toward telepharmacy among Indonesian pharmacists. However, the factors were not significantly correlated with the level of knowledge. These data contradict those of an Ethiopian study, which indicated that male gender and internet access were significantly associated with the knowledge of health professionals regarding telemedicine services.[39]

Table 5. Multivariate Analysis of Independent Determinants of Knowledge, Perception, and Readiness Toward Telepharmacy

	KNOWLEDGE		PERCEPTION		READINESS	
VARIABLES	*p* VALUE	aOR (95% CI)	*p* VALUE	aOR (95% CI)	*p* VALUE	aOR (95% CI)
Age						
17–25 years	–	Ref.	–	Ref.	–	Ref.
26–35 years	0.20	1.05 (0.89–1.23)	0.57	1.05 (0.89–1.23)	0.12	0.88 (0.75–1.03)
36–45 years	0.74	1.00 (0.83–1.20)	0.97	1.00 (0.83–1.20)	**<0.01**	0.73 (0.60–0.89)
>45 years	0.81	1.26 (0.97–1.65)	0.09	1.26 (0.97–1.65)	0.91	0.98 (0.74–1.30)
Gender						
Male	–	–	–	Ref.	–	Ref.
Female	–	–	**0.01**	0.83 (0.72–0.95)	**0.01**	0.83 (0.72–0.95)
Education level						
Pharmacist	–	Ref.	–	Ref.	–	Ref.
Master/doctoral	0.09	1.12 (0.90–1.40)	0.31	1.12 (0.90–1.40)	**0.01**	1.33 (1.06–1.67)
Field of work						
Community pharmacy	–	–	–	Ref.	–	Ref.
Hospital	–	–	0.89	1.01 (0.89–1.15)	0.15	1.11 (0.96–1.27)
Public health center	–	–	0.44	0.95 (0.83–1.09)	0.73	1.03 (0.89–1.18)
Internet access						
Stable	–	–	–	Ref.	–	Ref.
Unstable/Poor	–	–	**<0.01**	0.79 (0.67–0.92)	**<0.01**	0.75 (0.64–0.89)
Residence						
Rural	–	–	–	Ref.	–	Ref.
Urban	–	–	0.05	1.13 (1.00–1.28)	0.72	1.02 (0.90–1.16)
Region						
West region	–	–	–	Ref.	–	Ref.
Central region	–	–	**0.04**	1.16 (1.01–1.33)	**<0.01**	1.29 (1.12–1.49)
East region	–	–	0.65	0.93 (0.69–1.26)	**<0.01**	1.57 (1.16–2.12)

aOR, adjusted odds ratio; CI, confidence interval; Ref, reference.

$p < 0.05$ indicates statistical significance.

Moreover, our results revealed that male participants had a more positive perception toward telepharmacy than females. A stable internet access was also associated with better perception. Furthermore, pharmacists residing in the central region of Indonesia showed higher perceptions. A study conducted in Pakistan explored the perception and readiness of pharmacists toward the implementation of telepharmacy; gender, age, and field of work were significantly correlated with the perception of pharmacists.[33] Another study conducted in Jordan showed that male gender, age >35 years, and higher level of education are associated with a more positive attitude of pharmacists toward telepharmacy.[6]

Younger age, male gender, postgraduate education, stable internet access, and residing in the central region of Indonesia were correlated with higher levels of readiness. A study conducted in Saudi Arabia focused on KPR for telepharmacy among specialized hospital pharmacists. The results revealed that pharmacists with <5 years of

experience had a higher level of readiness versus those with ≥5 years of experience.[27] Moreover, a study examined the readiness of health professionals and associated factors for the implementation of telemedicine in Ethiopia. Among the sociodemographic characteristics, >5 years of work experience and internet access at the office were significantly associated with higher levels of readiness for the adoption of telemedicine.[40]

LIMITATIONS OF THE STUDY

The risk of selection bias in this study cannot be ignored, since the study involved the distribution of an online survey instrument through the WhatsApp groups of registered pharmacists at the national and provincial levels, who are members of pharmacy associations and societies in Indonesia. Moreover, pharmacists may be hesitant to provide honest responses that might damage their professional self-esteem and image. Nevertheless, the assurance of confidentiality may have helped to reduce this bias.

Despite these limitations, this study provides insight into the perception and readiness of pharmacists for telepharmacy. In addition, this first-of-its-kind study is strengthened by the inclusion of pharmacists from all provinces of Indonesia.

Conclusions

Indonesian pharmacists reported high levels of knowledge without significant influencing factors. However, they displayed moderate perceptions and readiness levels, influenced by sociodemographic factors. Gender, internet access, and region of residence were identified as independent determinants of the perception of pharmacists toward telepharmacy. Readiness was significantly associated with age, gender, internet access, education level, and region of residence. This evidence may guide health authorities in Indonesia to develop and implement telepharmacy policies.

Data Availability Statement

De-identified participant data can be made available upon requests directed via email to the corresponding author. The dataset used in this study can be made available on a reasonable request basis, which must include an appropriate protocol, analysis plan, and data exchange with institutional approvals in place before the data transfer of any information. This request needs to be formally addressed to the first author of the research group, Ikhwan Yuda Kusuma (ikhwanyudakusuma@uhb.ac.id).

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Authors' Contributions

Conceptualization: I.Y.K., K.I.K., and K.E.T.; methodology, formal analysis, software: I.Y.K., M.A.B., and M.M.; ethics and data collection: I.Y.K., K.I.K., K.E.T., A.A.K., and M.A.B.; investigation: I.Y.K., M.A.B., M.M., and R.B.; data curation and validation: Z.S., I.Z., M.M., and R.B.; writing—original draft preparation: I.Y.K., H.F.M., K.E.T., A.A.K., and M.A.B.; writing—review and editing: Z.S., I.Z., M.M., and R.B.; and funding acquisition: R.B. and I.Z. All authors have read and approved the final version of the manuscript.

Disclosure Statement

The authors declare no conflicts of interest.

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Supplementary Material

Supplementary Appendix S1
Supplementary Appendix S2
Supplementary Appendix S3
Supplementary Appendix S4
Supplementary Appendix S5

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