University of Szeged

Faculty of Pharmacy

Department of Clinical Pharmacy

CERTAIN ASPECTS OF PHARMACIST CONTRIBUTION AND DIFFERENT WAYS OF COMBATTING INFECTIOUS DISEASES

Ph.D. Thesis

Ikhwan Yuda Kusuma

Supervisors:

Dr. Ria Benkő, PhD
Dr. Mária Matuz, PhD

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GLOSSARY OF ABBREVIATIONS

AKAQ	Antibiotic Knowledge Assessment Questionnaire
ALT	Alanin aminotransferase
AMR	Antimicrobial resistance
aOR	Adjusted Odds Ratio
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
Ave	Average
bid	*bis in die* / two times a day
Comp	Comparator group
CDI	Clostridioides difficile infection
Chi2 (χ^2)	Chi-square test value (a measure of heterogeneity)
CI	Confidence Interval
COVID-19	Corona virus disease 2019
CVI	Content Validity Index
DDD	Defined Daily Dose
df	degrees of freedom
DIF	Differential Item Functioning
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
ESAC-Net	European Surveillance of Antimicrobial Consumption-Network
Favi	Favipiravir group
FDA	Food and Drug Administration
GPs	General Practitioners
HR	Hazard Ratio
I2	I-squared (a measure of heterogeneity)
IAI	*Ikatan Apoteker Indonesia*/ Indonesian Pharmacists Association
ICU	Intensive Care Unit
I-CVI	Item-Content Validity Index
IQR	Interquartile Range
J01	ATC code for antibacterials for systemic use
J01A	ATC code for tetracyclines
J01C	ATC code for beta-lactam antibacterials, penicillin
J01D	ATC code for other beta-lactam antibacterials
J01E	ATC code for sulfonamides and trimethoprim
J01F	ATC code for macrolides, lincosamides, and streptogramins
J01M	ATC code for quinolones
J01X	ATC code for other antibacterials
KPR	Knowledge, perception, and readiness
MNSQ	Mean-Square
OR	Odds Ratio
p	p-value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PRP	Penicillin-resistant pneumococci
PTMA	Point Measure Correlation
RCT	Randomized Controlled Trial

RD	Risk Difference
Ref	Reference
RR	Risk Ratio
RTI	Respiratory Tract Infections
RT-PCR	Reverse Transcription Polymerase Chain Reaction
S-CVI	Scale-level of Content Validity Index
SD	Standard Deviation
SMX/TMP	sulfamethoxazole and trimethoprim
SoC	Standard of Care
SpO2	Saturation of peripheral oxygen
SPSS	Statistical Package for the Social Sciences
STRAMA	Swedish strategic programme against antibiotic resistance
tau 2 (τ^2)	tau-squared (a measure of heterogeneity)
TdP	*torsades de pointes*
tid	*ter in die* / three times a day
UA	Universal Agreement
UTI	Urinary Tract Infections
WHO	World Health Organization
Z	Z-value
ZSTD	z-standard

LIST OF PUBLICATIONS

I. INTERNATIONAL JOURNALS

1. **Kusuma IY**, Matuz M, Bordás R, Haverinen MJ, Bahar MA, Hajdu E, Visnyovszki Á, Ruzsa R, Doró P, Engi Z, Csupor D, Benkő R. Antibiotic use in elderly patients in ambulatory care: A comparison between Hungary and Sweden. *Frontiers in Pharmacology*. 2022;13:1042418.
2. **Kusuma IY**, Bahar MA, Nuari DA, Prabandari R, Soeharto S, Csupor D. Antibiotic knowledge assessment questionnaire in undergraduate pharmacy students: A Rasch analysis of validity evidence. *Pharmacy Education*. 2024;24(1):54–78.
3. Bahar MA, **Kusuma IY**, Visnyovszki Á, Matuz M, Benkő R, Ferenci T, Szabó BG, Hajdú E, Pető Z, Csupor D. Favipiravir does not improve viral clearance in mild to moderate COVID-19–A systematic review and meta-analysis of randomized controlled trials. *Heliyon*. 2024;10(9).
4. **Kusuma IY**, Muddather HF, Kurnianto AA, Bahar MA, Kurniasih KI, Tololiu KE, Schelz Z, Zupkó I, Matuz M, Benkő R. Telepharmacy in Indonesia: Navigating knowledge, perception, and readiness among 6000 pharmacists and related sociodemographic determinants. *Telemedicine and e-Health.* 2024.

II. INTERNATIONAL CONFERENCES

1. **Kusuma IY**, Matuz M, Bordás R, Haverinen MJ, Bahar MA, Hajdu E, Visnyovszki Á, Ruzsa R, Doró P, Engi Z, Csupor D, Benkő R. 2022. Antibiotic Exposure of A Vulnerable Population: Consumption Of The Elderly. 4th International Conference on Pharmaceutical and Medical Sciences. Martin, Slovakia. September 16-18, 2022.
2. **Kusuma IY**, Matuz M, Bordás R, Haverinen MJ, Bahar MA, Hajdu E, Visnyovszki Á, Ruzsa R, Doró P, Engi Z, Csupor D, Benkő R. 2022. Outpatient fluoroquinolone use in elderly population of two European countries. European Drug Utilization Research Group (EuroDURG) Conference 2022. Prague, Czech Republic. October 19-21, 2022. Abs: *International Journal of Clinical Pharmacy*, 44 (6): 1553-1553.
3. Bahar MA, **Kusuma IY**, Visnyovszki Á, Matuz M, Benkő R, Ferenci T, Szabó BG, Hajdú E, Pető Z, Csupor D. 2022. The efficacy and safety of favipiravir in the treatment of nonsevere COVID-19: a systematic review and meta-analysis of randomized controlled trials. European Drug Utilization Research Group (EuroDURG) Conference 2022. Prague, Czech Republic. October 19-21, 2022. Abs: *International Journal of Clinical Pharmacy*, 44 (6): 1491-1491.
4. **Kusuma IY**, Bahar MA, Nuari DA, Prabandari R, Soeharto S, Csupor D. 2023. Antibiotic related knowledge of pharmacy students: questionnaire development and validation with Rasch analysis. European Drug Utilization Research Group Conference 2023. Bologna, Italy. July 27-30, 2023.

1. INTRODUCTION

Infectious diseases remain one of the most persistent and widespread public health challenges worldwide(1), particularly in low- and middle-income countries (LMICs), where health systems face critical barriers, including limited diagnostic infrastructure, constrained treatment access, and insufficient workforce capacity (1,2). The emergence and re-emergence of infectious pathogens, including antibiotic resistant bacteria or novel viruses , highlight the urgent need for global health preparedness and innovation in healthcare service delivery (3).

The COVID-19 pandemic has dramatically exposed vulnerabilities in health systems, supply chains and sparking a reevaluation of clinical preparedness and therapeutic strategies(4). Beyond the direct health impacts, the pandemic has disrupted routine health services and accelerated the shift toward digital healthcare(4). In parallel, the pandemic has reaffirmed the vital role of effective antimicrobials, especially antibiotics and antivirals, in infectious disease response and containment (5). However, theeffectiveness of antimicrobials is increasingly threatened by the rise of antimicrobial resistance (AMR)(6). The AMR crisis is driven by the inappropriate use of antimicrobials: overuse (lack of indication) suboptimal dosing, duration, etc. and generally the lack of adherence to stewardship guidelines. In 2019, bacterial resistance was associated with an estimated 4.95 million (3.62–6.57) deaths worldwide (7), and projections suggest this could rise to 10 million deaths annually by 2050 if no action is taken (2). In addition to clinical consequences, AMR imposes a significant economic burden on health systems and undermines the effectiveness of not only infectious disease management, but also other medical achievements such as surgical procedures, transplantation, chemotherapy, and intensive care, (2).

Drug utilization research (DUR) is essential to monitor antimicrobial prescribing patterns, identifying inappropriate practices, and guiding antimicrobial stewardship (AMS) policies (8). Pharmacists play a pivotal role in AMS programs, contributing through patient counseling, prescriber education, infection control, and drug utilization research (DUR) (9). Whether in hospital, community, or remote settings, pharmacists' active engagement in infectious disease control enhances treatment outcomes and supports rational antimicrobial use.

As mentioned above the pandemic has accelerated digital health transformation, including telepharmacy, which uses information and communication technology (ICT) to provide pharmaceutical care remotely (10,11). Telepharmacy enhances medication access in remote areas and facilitates real-time pharmacist-patient consultation (12,13), though implementation varies significantly across countries. It faces barriers such as lack of regulation, digital literacy gaps, and concerns over data security (12,13). Although its application increased during the pandemic (11), telepharmacy remains underutilized in many developing countries. The success of telepharmacy hinges on healthcare workforce readiness, particularly among pharmacists, as well as the presence of enabling policy and technological frameworks.

This thesis explores interconnected aspects of pharmacist contribution and ways of combatting infectious diseases, including antimicrobial stewardship, education, clinical intervention, and digital health approach. The research is structured around four interrelated studies, each addressing a specific challenge in infectious disease control.

1.1.Rationale for Study I: Antibiotic Use in the Elderly in Ambulatory Care

The elderly population in Europe is rising significantly. In 2019, 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 (14). The elderly population is at increased risk of many infectious diseases due to immunosenescence, a progressive decline in immune function (15). Despite the growing elderly demographic, comprehensive data on outpatient antibiotic use in elderly group remains scarce, particularly in ambulatory care settings. Existing studies are limited to a few countries, including Denmark (16), Norway (17), and the United States (18) and focus primarily on long-term care facilities (19). Understanding antibiotic use in ambulatory care among the elderly is crucial for developing strategies to combat AMR in this vulnerable population.

1.2.Rationale for Study II: AMR Knowledge Assessment in Pharmacy Students

Education and training of future healthcare professionals play a vital role in addressing AMR. The impact of AMR is more pronounced in low-middle income countries (2) compared to middle- or high-income countries due to weak laboratory capacity, inadequate health systems governance, limited health information systems, and constrained resources (20). Pharmacy students, as future stewards of antibiotic use, must possess foundational AMR knowledge (21–23). However, research on antibiotic knowledge among pharmacy students is limited, especially in developing countries (24–28). In Indonesia, studies have focused on the general population rather than pharmacy students (29–32), and a gap has not been addressed for Indonesian context, where Rasch analysis was utilized. Unlike the traditional factor analysis (29,33,34), Rasch analysis offers greater precision in evaluating structural validity of survey instruments (35). This study uses Rasch modeling to develop and validate the Antibiotic Knowledge Assessment Questionnaire (AKAQ) for Indonesian pharmacy students across 34 provinces, laying the groundwork for education policy reform in AMR training.

1.3.Rationale for Study III: Clinical Efficacy of Favipiravir in COVID-19

The COVID-19 pandemic has further underscored the importance of effective antimicrobials especially antiviral agents. Favipiravir, a broad-spectrum antiviral drug, was initially approved in Japan for treating influenza and later considered for COVID-19 treatment (36). Early studies, mainly from China faced methodological weaknesses (e.g. lack of randomization and blinding, heterogenous study population) (37,38), but subsequent trials led to its emergency use authorization in several countries during the COVID-19 pandemic (39,40). Despite this, favipiravir has not received approval from major regulatory bodies such as Food and Drug Administration (FDA) and European Medicines Agency (EMA) due to inconclusive efficacy results. Although multiple clinical trials and meta-analysis have been conducted, there is a lack of comprehensive assessments focusing on viral clearance time. Examining the efficacy of favipiravir in mild to moderate COVID-19 cases by systematically review and meta-analysis is crucial for understanding its potential role in treating this disease.

1.4.Rationale for Study IV: Telepharmacy Readiness in Indonesia

Indonesia, the largest archipelago in Southeast Asia with over 260 million people across 34 provinces, faces significant healthcare access disparities, especially in rural and island regions of the country (41,42). While telepharmacy was widely used during the COVID-19 pandemic

(10,11), it remains informally implemented and poorly integrated into national health systems. It also faces challenges such as reduced human interaction and data security concerns (12,13). Its success requires understanding pharmacist knowledge, perception, and readiness (KPR) for digital transformation.

Although telepharmacy is more prevalent in developed nations, few studies have assessed KPR related to telepharmacy implementation in developing countries (43–47). Telepharmacy offers a promising solution by enabling remote pharmaceutical care to patients residing in these underdeveloped areas(48,49) and reduce health inequalities (49,50). Pharmacists' KPR to telepharmacy play a crucial role in the successful implementation of telepharmacy services (10), informing design specific interventions for healthcare institutions, policymakers, and service providers.

2. OBJECTIVES

2.1. Comparison of outpatient antibiotic use in elderly population of Hungary and Sweden

2.1.1. To compare the scale, pattern and seasonality of antibiotic use in elderly patients in ambulatory care settings between Hungary and Sweden

2.2. Antibiotic knowledge assessment questionnaire in undergraduate pharmacy students

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

2.3. Favipiravir in treatment of mild to moderate COVID-19: A meta-analysis

2.3.1. To systematically review and meta-analyze the available evidence on the clinical efficacy and safety of favipiravir in treating mild to moderate COVID-19

2.4. Pharmacist's knowledge, perception, and readiness toward Telepharmacy

2.4.1. To investigate the level of knowledge, perception, and readiness among pharmacists for telepharmacy

2.4.2. To identify associated sociodemographic factors related to knowledge, perception, and readiness among Indonesian pharmacists toward telepharmacy.

3. METHODS

3.1. *Comparison of outpatient antibiotic use in elderly population of Hungary and Sweden*

3.1.1. Study Design and Setting

A retrospective and descriptive cross-national comparative study was conducted to collect data on antibacterial prescriptions dispensed at community pharmacies in Hungary and Sweden in 2017. Antibacterials were classified according to the anatomical therapeutic chemical (ATC) classification system defined by the World Health Organization (WHO) version 2022 (51). The use of systemic antibacterials (ATC: J01) was measured as prescriptions per 1000 inhabitants per year or per month. The study population included the elderly population (aged >65 years) of Hungary and Sweden in 2017, with 1,828,226 elderly individuals in Hungary and 1,976,857 in Sweden (data derived from Eurostat). These 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 in antibiotic consumption was also assessed.

3.1.2. 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 Swedish national health insurance systems cover almost 100% of their respective populations. 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). Approximately 95% of antibacterials are covered because non-reimbursed antibiotics are not included in the database. The Swedish database contains data on all dispensed antibiotic prescriptions, providing 100% drug coverage. It includes all medications prescribed to outpatients (irrespective of reimbursement status) that are issued by GPs, specialists, dentists, patients visiting private practices, or nursing homes.

3.1.3. Data Analysis

Statistical analyses were performed using Excel, and data visualization was conducted using the R package (version 4.1.2).

3.2. *Antibiotic knowledge assessment questionnaire in undergraduate pharmacy students*

3.2.1. Study Design, Participants, and Setting

Cross-sectional research with a quantitative method was performed in Indonesia from February to May 2022. The Antibiotic Knowledge Assessment Questionnaire (AKAQ) was developed as a self-administered tool using the Google Forms platform, accessible via internet browsers. The questionnaire was distributed online to undergraduate bachelor of pharmacy students (an education program before professional pharmacist education) with different semesters and universities.

3.2.2. Sample Size and Recruitment

The sample size was set to 500 participants. . 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 program. Data were transformed from the Google Form database into Statistical Package for the Social Sciences version 26.0 (52) to be exported into Winsteps version 5.2.1.0 software (53).

3.2.3. Instrument Development

The questionnaire development involved four steps, i.e., framework development, item (question) generation, item screening, and pre-testing (54). The framework utilized established questionnaires (26,55–57) and antimicrobial stewardship guidelines (58,59).

The AKAQ consisted of two parts. The first part collected demographic informations. The second part assessed participants' knowledge of antibiotics, covering three domains: general antibiotic knowledge (55,60), antibiotic resistance (26,56), and antibiotic stewardship (57–59). The questionnaire includes closed-ended questions with options of "agree," "do not agree," or "do not know," with true and false answers scored as 1 and 0, respectively. The "do not know" option was scored as 0, similar to "false".

Item screening involved four expert pharmacists with experience in teaching antibiotic-related subjects to pharmacy students. This process established the content validity of the AKAQ items and excluded questions that did not meet predetermined criteria. Content validity was assessed using the content validity index (CVI) approach, with Item-CVI (I-CVI), Scale-level CVI/Universal Agreement (S-CVI/UA), and Scale-level CVI/Average (S-CVI/Ave) achieving thresholds of $\geq$0.78, $\geq$0.8, and $\geq$0.9, respectively (61). Finally, a questionnaire comprising 29 items were constructed in Indonesian, consisting of 9 items under the general knowledge domain, 10 items under AMR, and 10 items under the antimicrobial stewardship domain (see Appendix 2.1).

3.2.4. Pre-testing

A pre-testing involving 30 pharmacy students was conducted to examine item clarity (62). Questionnaire items were corrected based on their feedback, and the polished version was used for validation. (see Appendix 2.2).

3.2.5. Construct Validity

The Rasch analysis was used to investigate the AKAQ validity based on construct validity. This psychometric technique enhances instrument precision, evaluates quality, and examines respondent performance (63). Psychometric parameters of the AKAQ, which were

assessed by validity parameters (item and person fit, and structural validity); reliability (person and item reliability, Cronbach's Alpha value; person and item separation); item-person interaction; and item bias using Differential Item Functioning (DIF) based on semester (Table 1).

3.2.6. Statistical Analysis

Winsteps version 5.2.1.0 software was used to perform Rasch analysis to check the validity and reliability of the AKAQ and to run a DIF analysis (53) and Statistical Package for the Social Sciences (SPSS) version 26(52) was used to run the descriptive statistics to describe the participant characteristics.

Table 1. Rasch measurement properties and assessment criteria

Rasch Measurement	Acceptable Range	Definition
Person and item fit analysis	Infit and outfit mean-square (MNSQ): 0.5–1.5(64,65). The value of 1.6 is accepted if an item has a positive point measure correlation (PTMA)(64,65). - Z-standard (ZSTD): −2 to +2 (can be ignored if sample size >200 (66).	Person and item fit were assessed using infit and outfit MNSQ and z-ZSTD values. Person fit identifies inconsistent response patterns (e.g., same response to all items). Item fit assesses whether each item accurately measures knowledge. Misfitting items should be revised or removed. Fit is visualized using a bubble chart..
Structural validity (unidimensionality)	Raw variances of >30%(67,68) Eigen values of <3(69)	Evaluates whether all items measure a single construct. Unidimensionality confirms structural validity by examining the proportion of variance explained by the items versus unexplained variance.
Reliability	Person and item reliability of >0.67(70) Cronbach's alpha value of >0.6(71)	Reliability is measured to indicate the reproducibility of the measure(33), (36).
Separation Coefficients for individual items and persons	Item separation value is expected as >3(69). Person separation values are 1.50 (acceptable), 2.00 (good), and 3.00 (excellent)(73,74)	Separation coefficients assess the instrument's ability to distinguish between different levels of respondent knowledge (person separation) and item difficulty (item separation). Higher values reflect better measurement precision.
Item-person interaction	Item-person interaction was assessed using the Wright map (Fig. 6), which displays item difficulty and participant ability on the same logit scale. A smaller distance between their mean values indicates better alignment. A difference close to 0 logits suggests a good match, while a difference greater than 1 logit reflects a mismatch in item difficulty and participant ability (75)	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) (76).	DIF analysis detects potential item bias (33) Students were grouped into (1st–5th semester) and (6th–12th semester) categories. Indonesian pharmacy programs typically span 8 semesters, students beyond this may be delayed in completing their studies.

3.3. *Favipiravir in treatment of mild to moderate COVID-19: A meta-analysis*

3.3.1. Study Design and Protocol

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement was used to guide the report of this meta-analysis (77). The study protocol was prospectively registered in PROSPERO under the reference number CRD4202232443 (www.crd.york.ac.uk).

3.3.2. Inclusion criteria

The patient, intervention, comparison, outcomes, and study design (PICOS) approach were used to answer our clinical questions and applied as follows: P: COVID-19 patients with mild-to-moderate conditions, I: favipiravir, C: placebo/standard of care/another antiviral drug, O: time to viral clearance, S: randomized, controlled trials. The classification of mild and moderate illness in the papers was based on the descriptions provided by the World Health Organization (WHO) (78). 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 ≥ 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 hours. 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 hours. 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, diarrhoea, dizziness, dyspnoea, dyspepsia, headache, myalgia, nasal congestion, nausea, rhinorrhoea, skin rash, and vomiting.

3.3.3. 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 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 including published systematic reviews and meta-analyses on favipiravir. Only full-text articles were included, with no language restrictions. Duplicate records were removed using Rayyan (http://rayyan.qcri.org). The complete search queries are provided in the Appendix 3.1.

3.3.4. Record screening

The titles and abstracts of selected papers from each database were first screened by two independent reviewers. To reach a consensus, the conflicting screening results were discussed and the opinion of a third reviewer was sought. Two authorsthen 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.

3.3.5. Data extraction

Data were extracted independently by two reviewers using a pre-piloted data extraction form. Information extracted included 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 parameters.

3.3.6. 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 (79). The appraisal of study quality was done by two reviewers separately. Disagreements between the two reviewers were resolved by discussion and the participation of the third reviewer was considered if no consensus was reached.

3.3.7. 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 Appendix 3.2) that made it possible to directly calculate HR under the assumption that patients who once had undetectable viral load will remain undetectable (80). Sensitivity analyses were conducted to assess the impact of excluding specific studies (Appendix 3.2). 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 (81). 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.

3.4. *Pharmacist's knowledge, perception, and readiness toward Telepharmacy*

3.4.1. 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 were considered eligible.

3.4.2. Instruments

A 24-item instrument was used to investigate Knowledge, Perception, and Readiness (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. (Appendix 4.1. and 4.2.) was used (82). Knowledge was assessed using eight items (Cronbach's alpha = 0.961). Responses to knowledge statements included "*yes*" or "*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), and readiness was assessed using another eight items (Cronbach's alpha = 0.931). Both perception and readiness were rated using a 5-point Likert scale (1 = *strongly disagree*, 2 = *disagree*, 3 = *neutral*, 4 = *agree*, 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 following formula was used: (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%. Additionally, 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 indicated higher KPR. The score for each domain was calculated based on the mean score of items within that domain(83). Scores <50%, 50–70%, and >70% indicate low, moderate, and high levels of KPR, respectively (29).

3.4.3. Ethical approval

The survey-based study was approved by the Health Research Ethics Committee of Universitas Harapan Bangsa, Indonesia (approval number: B.LPPM-UHB/955/05/2022).

3.4.4. Procedures

Data collection involved several steps. First, we sent a request letter to the Central Indonesian Pharmacists Association (*Ikatan Apoteker Indonesia Pusat* [IAI]). Second, after obtaining permission from the IAI Central, the IAI 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; the provinces were divided into three regions according to the time zone. The study flow diagram is presented in Figure 1.

3.4.5. Data analysis

All analyses were performed with the Statistical Package for Social Sciences Software (SPSS), version 26.0 (SPSS, IBM Corp., Armonk, NY, USA). Descriptive statistics were used to analyze the sociodemographic characteristics of the participants. Categorical variables were presented as numbers and percentages, while continuous variables were 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-value < 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-values < 0.05 denoting statistical significance.

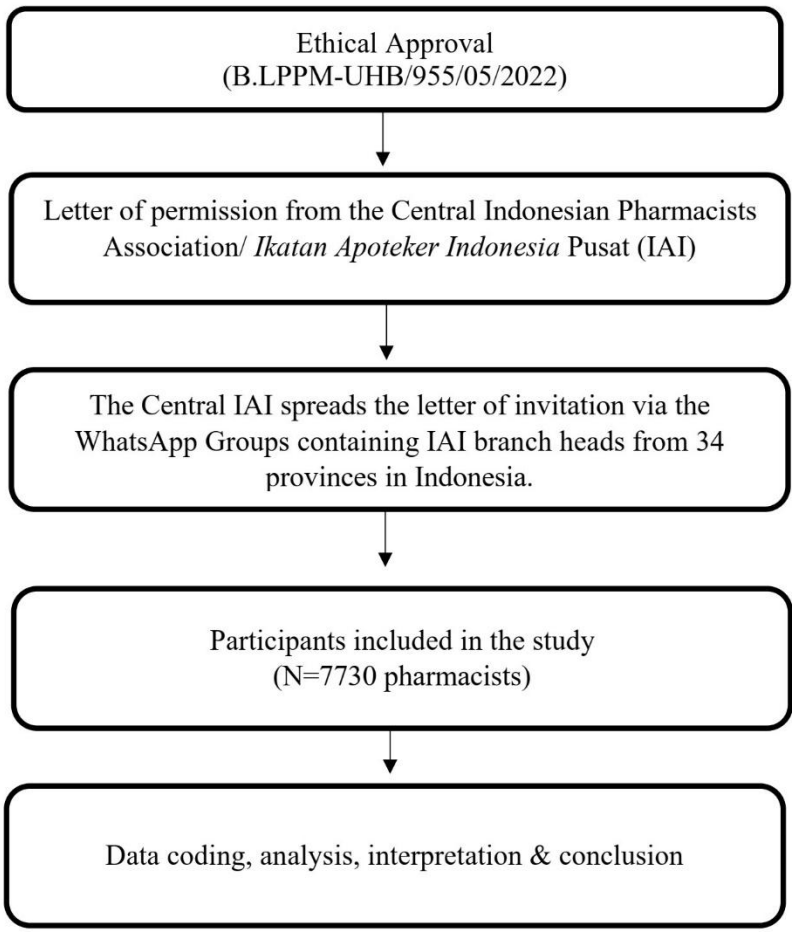

Figure 1. Study flow diagram. IAI = *Ikatan Apoteker Indonesia Pusat* (Central Indonesian Pharmacists Association). N = number of respondents.

4. RESULTS

4.1. *Comparison of outpatient antibiotic use in elderly population of Hungary and Sweden*

4.1.2. 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 2 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.

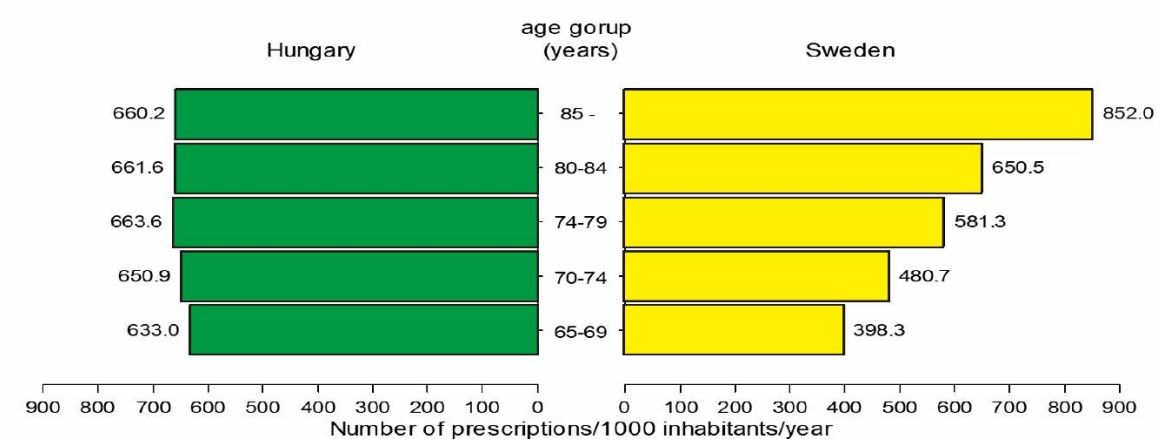

Figure 2. Antibacterial use in different elderly age subgroups in Hungary and Sweden (2017)

4.1.2. The Pattern of Antibiotic Use

Table 2 shows the absolute and relative use of different antibacterial subgroups. Concerning the beta-lactam antibacterials, the penicillin group was responsible for one-fifth of total ambulatory care antibiotic use in the elderly in Hungary, and cephalosporins also had considerable use and share. In contrast, the penicillin group was responsible for almost half of antibiotic use in the elderly in Sweden, 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 2).

Table 3 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, 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.

Table 2. Absolute and relative use of 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	*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 Sulfonamides & trimethoprim Combinations	*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	*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

Table 3. 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
amoxicillin/ clavulanic acid	123	18.95	phenoxymethyl penicillin	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
SMX/TMP*	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

4.1.3. 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 (Figure 3).

However, the antibiotic exposure of the two sexes of the elderly population showed opposite trends in the age subgroup analysis in Hungary (Figure 3). 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 (Figure 2 and Figure 3) and in all elderly subgroups Swedish females were exposed to more antibiotics than Swedish males).

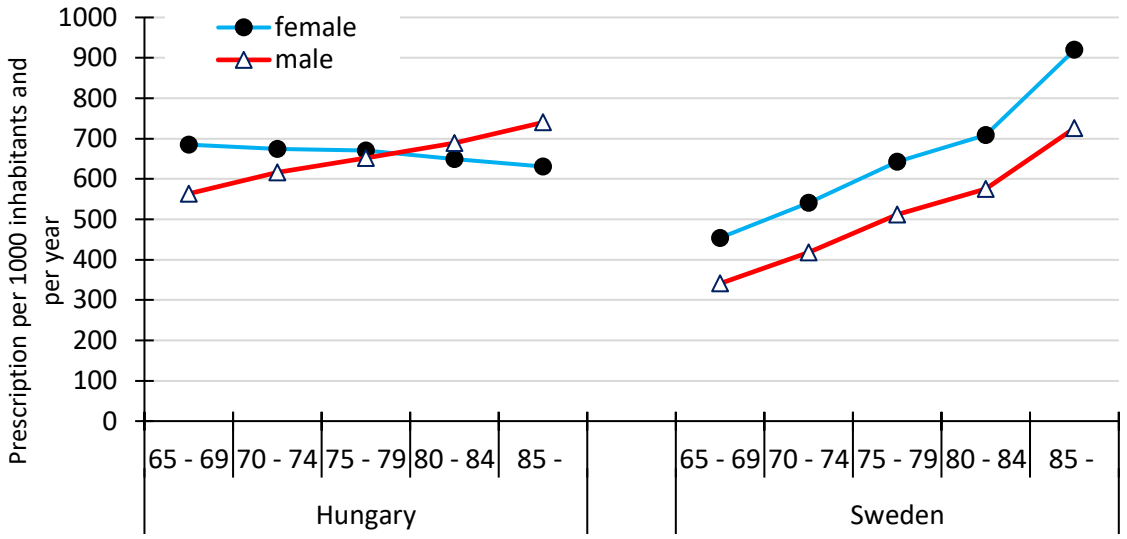

Figure 3. Sex-specific use of antibiotics in ambulatory care presented by age subgroups in the elderly population in Hungary and Sweden (2017)

4.1.4. Seasonal Variation

Figure 4 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/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.

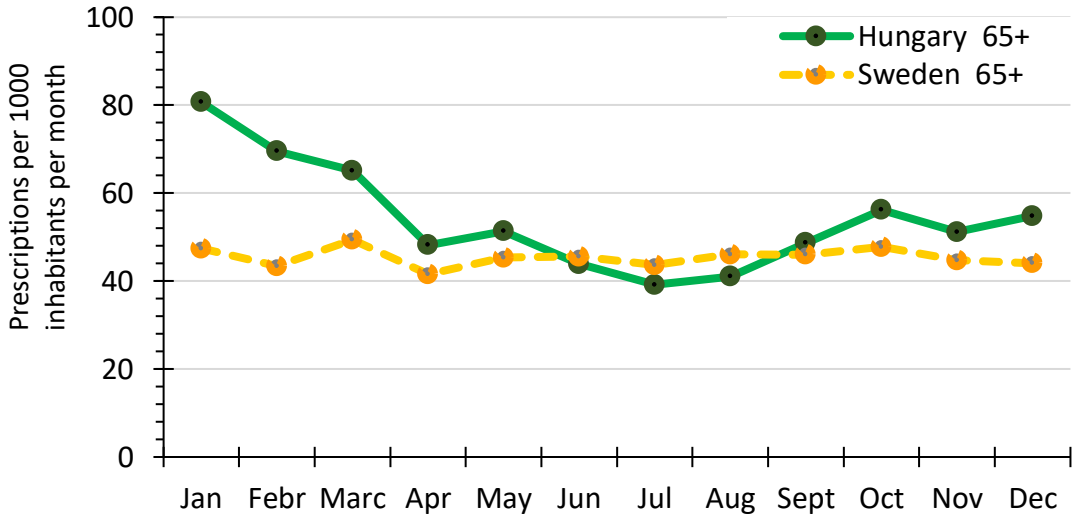

Figure 4. Seasonal variation of antibiotic use among the elderly population in Hungary and Sweden in 2017

4.2. *Antibiotic knowledge assessment questionnaire in undergraduate pharmacy students*

4.2.1. Data Collection and Screening

A total of 500 AKAQ participants from 90 Indonesian universities completed the questionnaire (Table 4). Among the participants, 85% were females; 59% were 20–23 years old; 30.4% were in the fourth semester. Most participants (69.0%) were from universities in the western region of Indonesia where most of the universities are located.

Table 4. 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%
Semester		
1^{st} – 5^{th} Semester	282	56.4%
6^{th} – 12^{th} Semester	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%

4.2.2. AKAQ Validity and Reliability

The Person and Item Fit Parameters are summarized in Table 5. Overall, the average of infit (weight) and outfit (unweight) mean square (MNSQ) values (0.93 and 1.00), and z-standard (ZSTD) (0.03 and 0.06), were within acceptable thresholds. However, 11% of participants (n = 56) were misfits (see Appendix 2.3) (infit/outfit MNSQ outside 0.5–1.6 with positive PTMA) (64,65) and were excluded. After deletion, fit statistics improved with MNSQ and ZSTD person values were 0.95 and 1.02, and 0.11 and 0.08, respectively. For item fit statistics, all mean values were within recommended boundaries (infit MNSQ = 1.00, outfit MNSQ = 0.93; ZSTD = −0.30 and 0.09, respectively) except one misfitting item (K7; MNSQ: 0.17; ZSTD: −2.18) (see Appendix 2.4), which was subsequently removed (see Appendix 2.5). Post-deletion, item fit indices improved across both MNSQ and ZSTD (see Table 5). Although 10 misfit items exceeded the ZSTD threshold (see Appendix 2.4), this is acceptable for large sample sizes (>200) (66). Final 28 items fit orders are shown in Figure 5.

The Y-axis represents item difficulty based on Joint Maximum Likelihood Estimation, and the X-axis shows Item Fit MNSQ (69). Each bubble corresponds to an item, with its size proportional to the standard error of item difficulty calibration. Items that fall close to the vertical line indicate good fit, with outfit MNSQ values in the acceptable range (x = 0.50–1.50). Items with MNSQ values exceeding 1.50 indicate overfit (64).

Table 5. The Summary of Rasch Parameters for AKAQ

	Persons	Person (After deletion of 56 person misfits)	Item (question)	Item (After deletion item 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	1.02	1.00	1.01
	(0.43-1.69)	*(0.61-1.69)*	*(0.82-1.16)*	*(0.89-1.16)*
Infit ZSTD	0.03	0.11	0.09	0.11
	(-2,85-2.5)	*(-1.90-2.44)*	*(-2.72-4.46)*	*(-2.72-4.46)*
Outfit MNSQ	0.93	0.95	0.93	0.96
	(0.14- 2.73)	*(0.50-1.58)*	*(0.17-1.24)*	*(0.73-1.24)*
Outfit ZSTD	0.06	0.08	-0.30	-0.23
	(-1.33-2.80)	*(-1.13-1.27)*	*(-2.55-2.85)*	*(-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

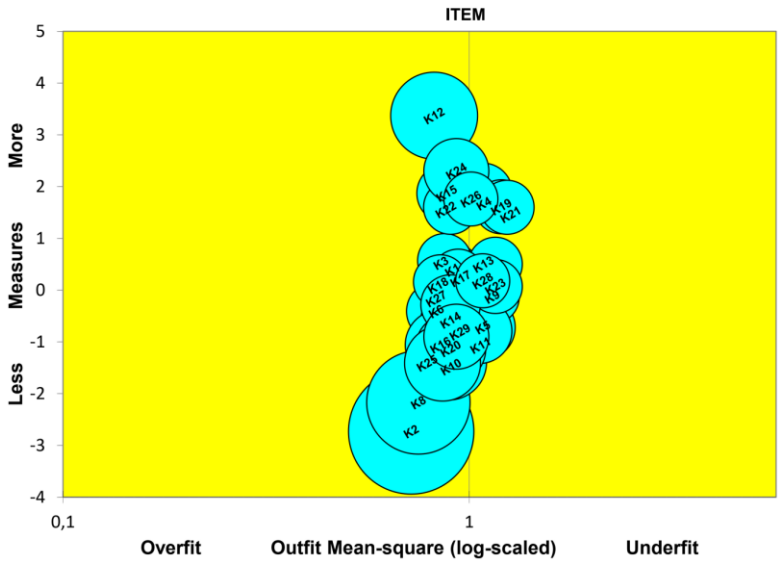

Figure 5. Bubble Chart of Item Fit Order

4.2.3. Construct validity (unidimensionality)

The structural validity of the AKAQ was further examined using unidimensionality. The results achieved an acceptable threshold at >30%(67,68) (33.4%), which indicates that the instrument achieves 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.

4.2.4. 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(71) (Table 5). Overall, the AKAQ exhibited acceptable criteria for the Rasch reliability parameter (70,71). 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(74,84).

4.2.5. Item-person interaction

We presented the item-person Wright map in Figure 6 to check whether the items in the AKAQ are 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 items (69). The difference between the mean person measure and the mean item measure was <1 logit (0.51 logits), indicating that the difficulty level of the items was suitable for the participants' abilities (67,69). Hence, we can identify that the item K2 (Bacterial infections can be treated with antibiotics) was the easiest item and item 12 (Beta-lactamases are enzymes produced by bacteria that break open the beta-lactam ring) was the hardest (85).

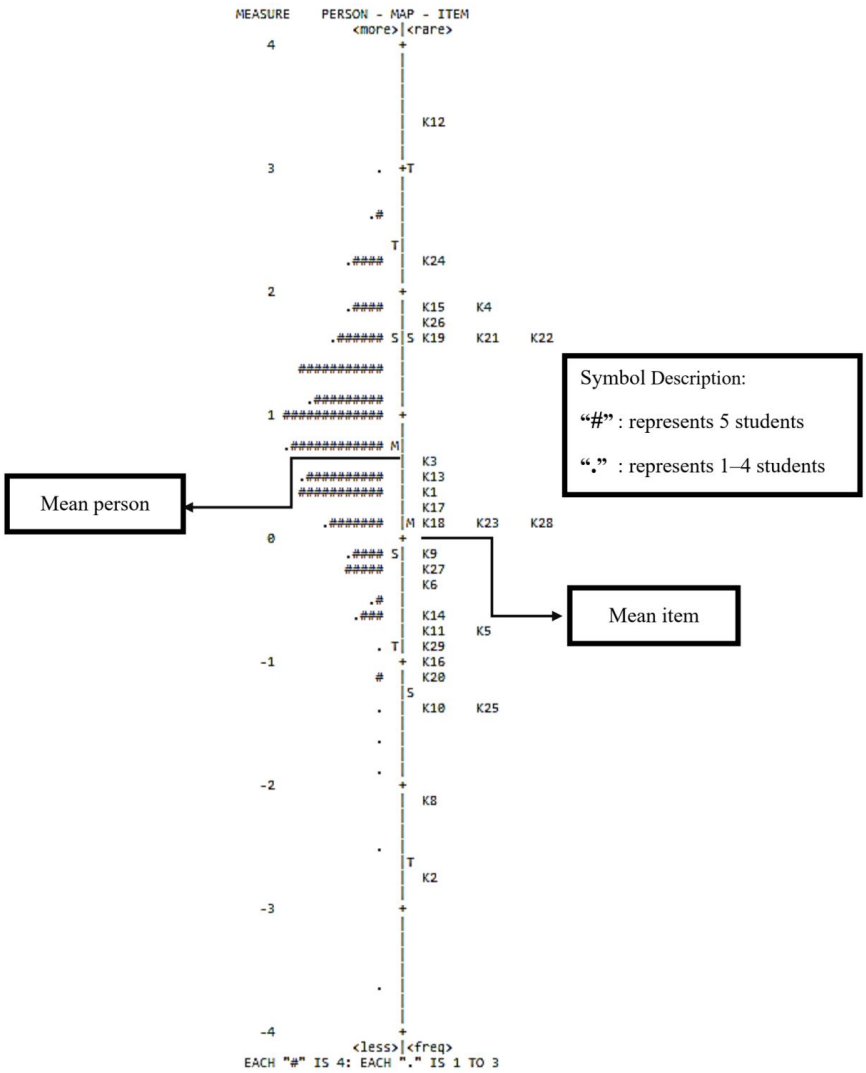

Figure 6. Wright Map (Item-Person Correlation).

The Wright map also shows that students had >50% chance (p = 0.5) of correctly answering an item when their indicator was above the item's indicator. A 50% chance (p = 0.5) occurred when the indicators aligned, indicating comparable difficulty levels between the item and the student's ability. Conversely, students had <50% chance (p < 0.5) of correctly answering the item if their indicator was below the item's indicator.
This map displays the distribution of person ability and item difficulty on the same logit scale. The left side represents individual respondents, with higher positions indicating greater ability. Each "#" symbol denotes five students, and each point "." represents one to four students. The right side displays the 28 questionnaire items, ranked from the easiest (K2, at the bottom) to the most difficult (K12, at the top). The letter "M" indicates the mean person ability (left) and mean item difficulty (right). Items and persons that align closely to the center vertical axis reflect a good match between item difficulty and participant ability (75).

4.2.6. Differential Item Functioning (DIF) Analysis

DIF analysis by semester (Figure 7) indicated that the items K6 (DIF:0.79; Prob:0.0045) and K19 (DIF: −0.67; Prob: 0.0198) have moderate to large DIF category(76) (see Appendix 2.6). Items K6 and K19 were found to be relatively easier for students in earlier semesters (1st–5th) compared to those in later semesters (6th–12th). This may reflect better recall of basic knowledge recently covered in coursework or greater attentiveness to core topics in the early years of study. However, these items were not dropped because they are relevant to antibiotic-related knowledge, as indicated by content and construct validity results. Dropping these items might reduce the reliability and validity (84).

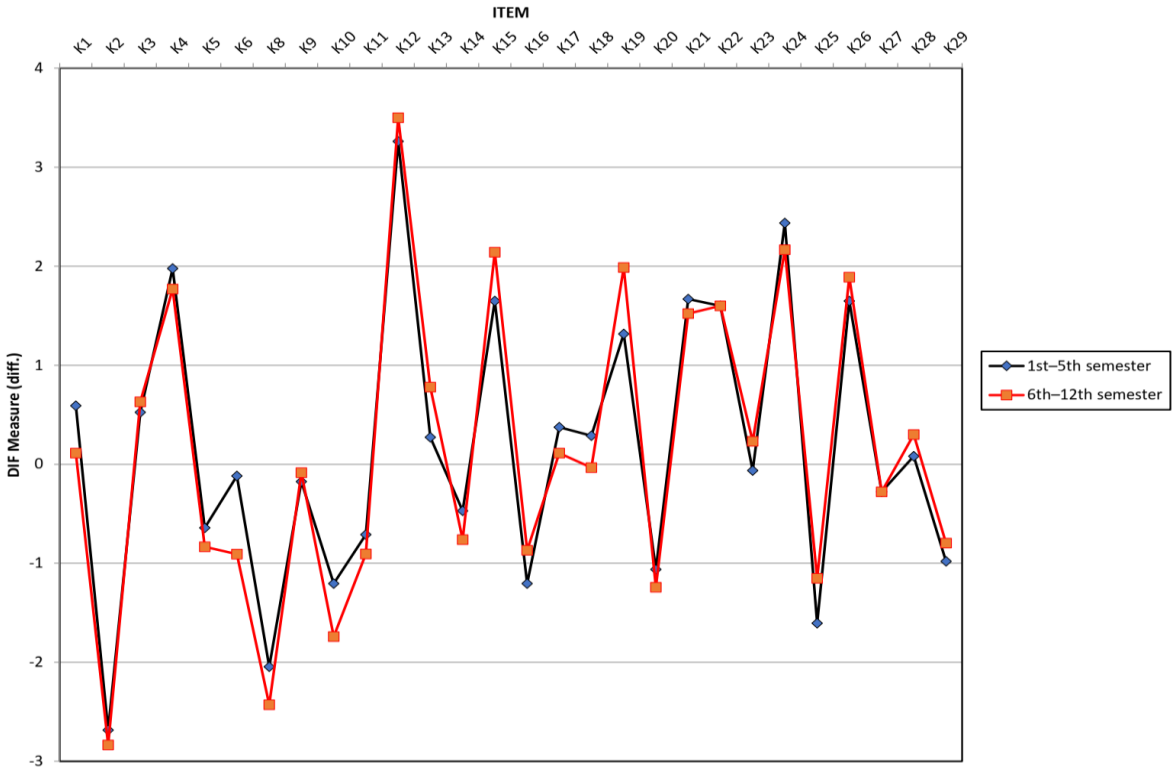

Figure 7. DIF Based on the Semester

4.3. *Favipiravir in treatment of mild to moderate COVID-19: A meta-analysis*

4.3.1. 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), not eligible study design (n=14), abstract proceeding (n=3), favipiravir combined with another antiviral drug (n=5), wrong comparison (n=1), not eligible disease severity (n=3), and a parenteral drug administration (n=1). Therefore, the final number of articles included was 20 (Figure 8). Reviewer agreement was high: 99.5% at the title/abstract level ($\kappa = 0.71$, good) and 96.4% at full-text screening ($\kappa = 0.93$, very good).

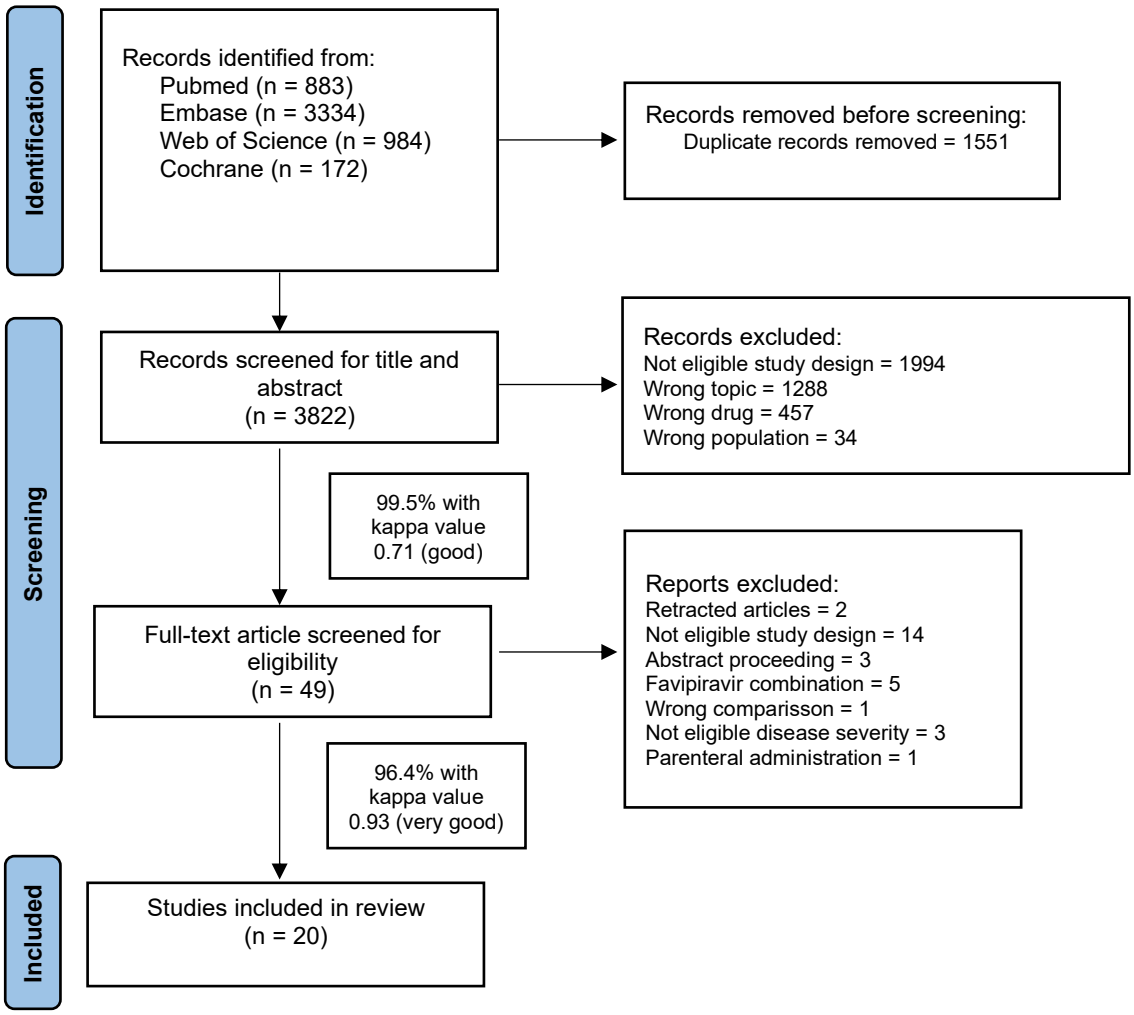

Figure 8. Flow chart of study selection

4.3.2. Study characteristics

Among the 20 eligible articles, 12 were open-label, seven were double-blind, and one was single-blind randomized controlled trials, all involving patients with mild to moderate COVID-19. Study locations were diverse: four in Russia, three in China, and one each in Australia, Bahrain, Bangladesh, India, Iran, Japan, Kuwait, Malaysia, Saudi Arabia, Thailand, the UK, and the USA. One study included multiple countries (Brazil, Mexico, and the USA). Thirteen studies were conducted in inpatient settings, five in outpatient settings, and two in both. All studies administered a loading dose of oral favipiravir on day one (1600–2200 mg, two to three times daily), followed by 1200–1800 mg daily in divided doses for 5 to 14 days. In most studies, randomization occurred within 12 days of symptom onset. The characteristics and outcomes of each study are summarized in Table 6 and Appendix 3.3, respectively. However, three studies did not report the randomization method, and four lacked information on allocation concealment. Additionally, 12 studies were unblinded. A summary and visual representation of the risk of bias are provided in Figure 9 and Appendix 3.4.

4.3.3. Methodological assessments of articles

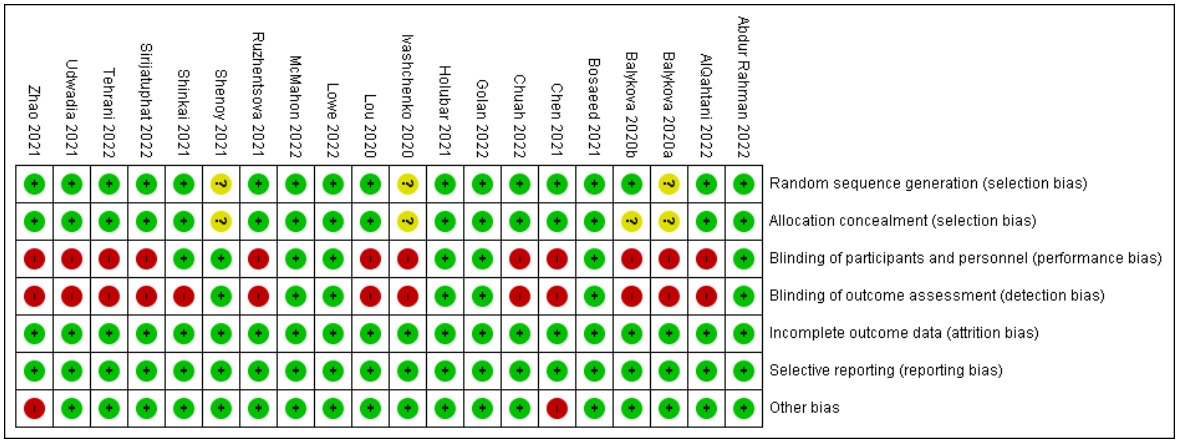

Figure 9. Risk of bias summary of included studies

4.3.4. Primary efficacy outcomes

There were eight studies that reported the Hazard Ratio (HR) for viral clearence (80,90,93,97,99,100,102,103) (Appendix 3.3). There were no statistically significant differences between the favipiravir and comparator groups in viral clearance (HR = 1.20 [95% CI (Confidence Interval): 0.98-1.47, p=0.09], I^2 (I-squared heterogeneity statistic)=40%) (Figure 10). 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 to the comparators in patients with moderate severity of COVID-19 (Figure 11). 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 (Figure 11).

Table 6. Characteristics of eligible studies

Ref.	Country	Study Design	Number of patients		Age			Sex (Male in %)	Severity	Setting of care	Favipiravir dose	Comparator	Onset to randomization
			Favipiravir (Favi)	Comparator (Comp)	Mean in years(SD)	Median in years (IQR)	Quantity (< 65 years, %)						
Abdur Rahman, 2022(86)	Bangladesh	Double-blinded randomized controlled trial	25	25	Favi: 37.96 (11.45) Comp: 37.54 (10.18)			Favi: 64 Comp: 68	Mild and Moderate	Inpatient	1st day: 1600 mg (bid) 2nd – 10th day: 600 mg (bid)	Placebo	Within 7 days
AlQahtani, 2022(87)	Bahrain	Randomized, controlled, open-labeled study	54	51		Favi: 44.5 (33.0, 50.0) Comp: 48.5 (35.5, 57.0)		Favi: 43 Comp: 52	Mild and Moderate	Inpatient	1st day: 1600 mg (bid) 2nd – 10th day: 600 mg (bid)	SoC	Within 10 days
Balykova,2020a(88)	Russia	Randomized, open-label, multicenter comparative study	17	22	Favi: 47.1 (2.3) Comp: 47.5 (1.9)			No Infaviormation	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 hours before administration of favipiravir
Balykova, 2020b(89)	Russia	Open randomized multicentre comparative study	100	100	Mean Age Ofavi Population: 49.7 (13.1) Range Ofavi Age: 20 To 80			Favi: 50.9 Comp: 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 hours before the start of the study
Bossaed, 2021(90)	Saudi Arabia	Randomized double-blinded, multicentre placebo-controlled trial	112	119		Favi: 37 (31.5, 45.0) Comp: 37 (32, 44)		Favi: 64.2 Comp: 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(38)	China	Randomized controlled, open-label multicenter trial	116	120			Favi: 75 Comp: 65.8	Favi: 50.9 Comp: 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

Ref.	Country	Study Design	Number of patients		Age			Sex (Male in %)	Severity	Setting of care	Favipiravir dose	Comparator	Onset to randomization
			Favipiravir (Favi)	Comparator (Comp)	Mean in years(SD)	Median in years (IQR)	Quantity (< 65 years, %)						
Chuah, 2022(91)	Malaysia	Randomized, open-label, parallel, multicenter, phase 3 clinical trial	250	250	Favi: 62.6 (7.51) Comp: 62.4 (8.41)			Favi: 52.4 Comp: 44.4	Mild to moderate	Inpatient	1st day: 1800 mg (bid) 2nd – 5th days: 800 mg (bid)	SoC	Within 7 days
Golan, 2022(92)	USA, Brazil, Mexico	Randomized, multicenter, double-blind, placebo-controlled trial	599	588			Favi (<60, %): 84.5 Comp (<60, %): 86.1	Favi: 47.1 Comp: 44.4	Mild to moderate	Outpatient	1st day: 1800 mg (bid) 2nd – 10th days: 800 mg (bid)	Placebo + SoC	Within 5 days
Holubar, 2021(93)	USA	Randomized, double-blind, placebo-controlled phase 2 trial	59	57	Favi: 42.9 (12.3) Comp: 43.4 (12.8)			Favi: 52.5 Comp: 49.1	Mild	Outpatient	1st day: 1800 mg (bid) 2nd – 10th day: 800 mg (bid)	Placebo + SoC	Positive SARS-CoV2 RT-PCR within 72 hours of enrollment
Ivashchenko, 2020(94)	Russia	Randomized, adaptive, multicenter, open-label, Phase II/III clinical trial	40	20		No Infaviormation		No Infaviormation	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(95)	China	Randomized, exploratory single-center, open-label, controlled trial	9	10	Favi: 58.0 (8.1) Comp: 46.6 (14.1)			Favi: 77 Comp: 70	Mild to Moderate	Inpatient	1st day : 1600 mg or 2200 mg (tid) 2nd – 14th days: 600 mg (tid)	SoC	No information
Lowe, 2022(80)	UK	Randomized, Double-blind, 2x2 factorial placebo-controlled trial	59	60	Favi: 40.3 (12.1) Comp: 40.6 (12.2)			Favi: 54.2 Comp: 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(96)	Australia	Randomized placebo-controlled phase 2 trial	66	67		Favi: 36 (28-49) Comp: 35 (27.5, 52.5)		Favi: 55.6 Comp: 54	Mild and Moderate	Inpatient and Outpatient	1st day: 1800 mg (bid) 2nd – 14th day: 800 mg (bid)	Placebo + SoC	Within 5 days

Ref.	Country	Study Design	Number of patients		Age			Sex (Male in %)	Severity	Setting of care	Favipiravir dose	Comparator	Onset to randomization
			Favipiravir (Favi)	Comparator (Comp)	Mean in years(SD)	Median in years (IQR)	Quantity (< 65 years, %)						
Ruzhentsova, 2021(97)	Russia	Randomized, open-label, active-controlled trial	112	56	Favi: 41.7 (10.6) Comp: 42.0 (10.4)			Favi: 43.8 Comp: 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(98)	Kuwait	Randomized, multicentre, double-blind, placebo-controlled, parallel design	175	178			Favi (<50, %): 40 Comp (<50, %): 41.6	Favi: 67.4 Comp: 67.4	Moderate	Inpatient	1st day : 1800 mg (bid), 2nd – 10th day: 800 mg (bid)	Placebo + SoC	Within 10 days
Shinkai, 2021(99)	Japan	Randomized, single-blind, placebo-controlled, parallel-group design	107	49	Favi: 43.8 (12.5) Comp: 48.7 (14.1)		Favi: 94.4 Comp: 85.7	Favi: 71.0 Comp: 57.1	Moderate	Inpatient	1st day: 1800 mg (bid) 2nd – 13th day: 800 mg (bid)	Placebo + SoC	Within 10 days
Sirijatuphat, 2022(100)	Thailand	Multicentre, open-labelled, randomized control study	62	31		Favi: 32 (27-39) Comp: 28 (25, 35)		Favi: 33.9 Comp: 38.7	Mild	Inpatient	1st day: 1800 mg (bid) 2nd – 14th day: 800 mg (bid)	SoC	Within 10 days
Tehrani, 2022(101)	Iran	Randomized, open-label, controlled clinical trial,	38	40	Favi: 53.08 (11.80) Comp: 51.95 (13.34)			Favi: 52.6 Comp: 57.5	Moderate	Outpatient	1st day: 1600 mg (bid) 2nd – 4th day: 600 mg (bid)	SoC	Within 3-9 days
Udwadia, 2021(102)	India	Randomized, open-label, parallel-arm, multicenter trial	72	75	Favi: 43.6 (12.2) Comp: 43.0 (11.2)			Favi: 70.8 Comp: 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(103)	China	Multicenter open-label, randomized controlled trial	36	19	Favi: 55.8 (13.6) Comp: 55.5 (12.6)			Favi: 44.4 Comp: 47.4	Mild and Moderate	Inpatient	1st day: 1600 mg (bid) 2nd – 7th days: 600 mg (bid)	SoC	No information

Abbreviations: Favi = Favipiravir group; Comp = Comparator group; SoC = Standard of Care; RCT = Randomized Controlled Trial; bid = twice daily; IQR = Interquartile Range; SD = Standard Deviation.

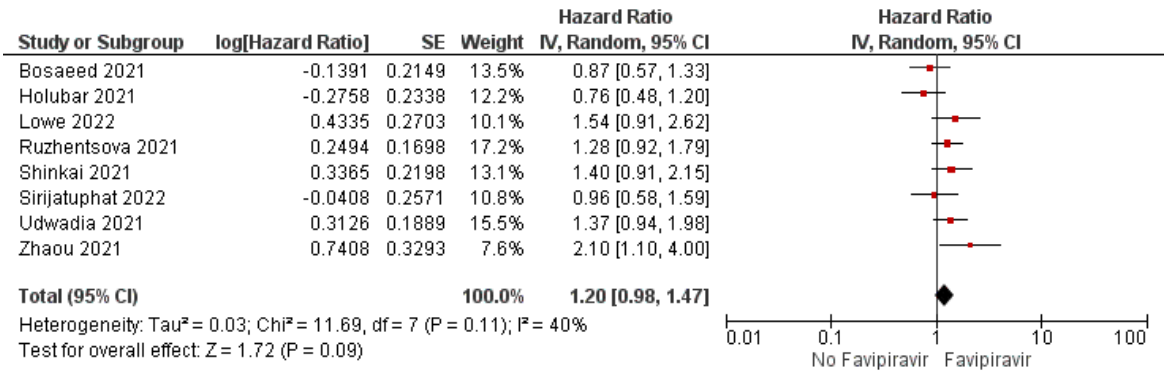

Figure 10. Favipiravir had no significant effect on viral clearance compared to comparator

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 (Appendix 3.5). 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 (Appendix 3.5).

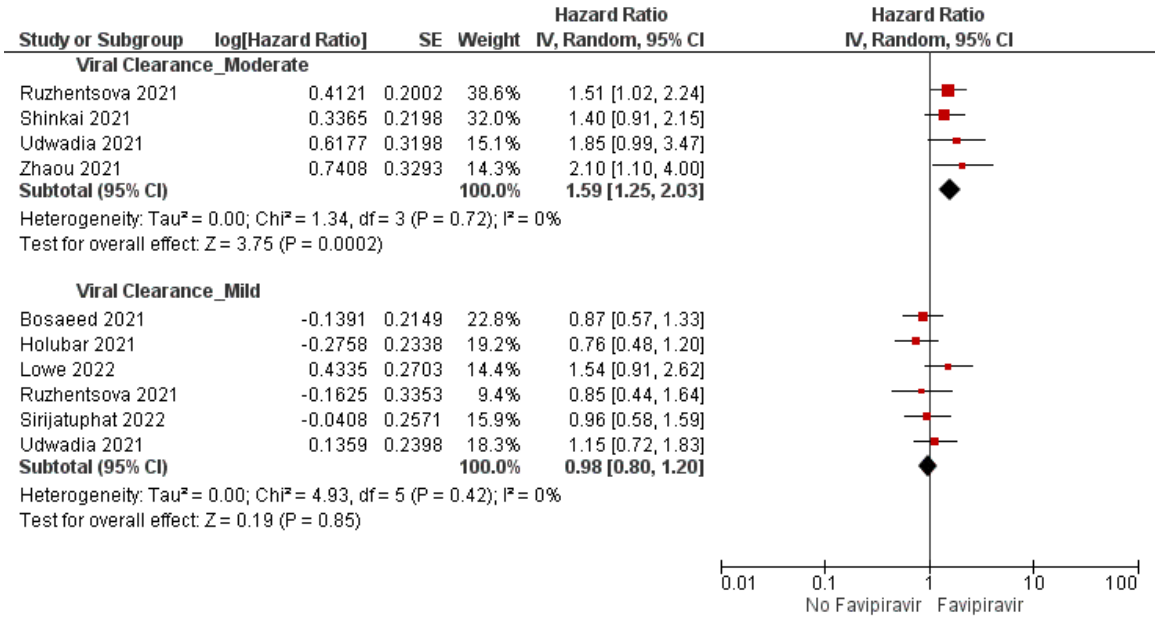

Figure 11. Favipiravir was more effective in terms of viral clearance in moderate, but not in mild severity.

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 relative risk (RR) for viral clearance (80,86–90,92–95,99,102,103) (Appendix 3.3). Achieved 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 (Appendix 3.6.a and Appendix 3.7.a). 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 (Appendix 3.6.b and Appendix 3.7.b).

4.3.5. 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 7). 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 (38,89,99,102). 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 (100). Another study did not have a subgroup analysis by severity (97,101).

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 (90,91,93,95,98,102). There studies did not provide a subgroup analysis by severity (87,92,96).

All studies reported at least one of the other secondary outcomes that can be pooled in the meta-analysis (Appendix 3.3). 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 (Appendix 3.8a). 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%), hospitalization's (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%) (Appendix 3.8b-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%) (Appendix 3.8g).

Table 7. Effects of favipiravir on clinical improvement

Reference	Parameters	Results		
		Overall severity COVID-19	**Mild severity COVID-19**	**Moderate severity COVID-19**
Favorable for favipiravir (Favi)				
Balykova, 2020b(89)	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 ; FAVI: 90% SoC: 67%
Chen, 2021(38)	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 FAVI: 71.43% SoC + Umifenovir: 55.86% Rate ratio: 0.1557 (95% CI: 0.03-0.28, p value=0.02)
Ruzhentsova, 2021(97)	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 FAVI: 6 days (IQR: 4-9.25 days) SoC: 10 days (IQR: 5-21 days) RR: 1.26, 95% CI: 1.02-1.54 FAVI: 83.03% SoC: 66.10%		HR: 1.66, 95% CI: 1.09-2.52
Shinkai, 2021(99)	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 FAVI: 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 FAVI: 75.70% SoC: 57%
Sirijatuphat, 2022(100)	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 FAVI: 2 days Control: 14 days Range of 1–28 days for both groups RR: 2.45, 95% CI: 1.45-4.15 FAVI: 79% SoC: 32.3%	
Tehrani, 2022(101)	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(102)	Time to clinical cure: according to clinician assessment and clinical	HR: 1.75, 95% CI: 1.10- 2.79 Median time		HR: 2.09, 95% CI: 1.06-4.15 Median time

Reference	Parameters	Results		
		Overall severity COVID-19	**Mild severity COVID-19**	**Moderate severity COVID-19**
	parameters such as normalization of fever, respiratory rate, oxygen saturation as well as cough relief persisted for ≥72 h.	FAVI: 3 days (95% CI: 3-4 days) Control: 5 days (95% CI: 4-6 days) RR: 1.02, 95% CI: 0.94-1.12 FAVI: 96.22% SoC: 93.90%		FAVI: 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 FAVI: 95.83% SoC: 87.50%
Unfavorable for favipiravir (FAVI)				
AlQahtani, 2022(87)	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 FAVI: 83.33% SoC: 80.77%		
Bosaeed, 2021(90)	Time to clinical recovery: normalization of temperature and respiratory symptoms, as well as the suppression of the cough, persisted for at least 72 hours.	-	HR: 0.89, 95% CI: 0.64-1.25 Median time FAVI: 7 days (IQR: 4-11 days) Placebo+SoC: 7 days (IQR: 5-10 days)	-
Chuah, 2022(91)	Rate of clinical progression from nonhypoxia to hypoxia	RR:1.24, 95% CI: 0.84–1.85 FAVI: 18.40% SoC: 14.80%	RR: 1.38, 95% CI: 0.71-2.67 FAVI: 14.84% SoC: 10.74%	RR: 1.01, 95% CI: 0.60-1.70 FAVI: 18.85% SoC: 18.60%
Golan, 2022(92)	Time to sustained clinical recovery: based on oxygen saturation, oral temperature, and all COVID-19-associated symptoms for four consecutive days	Median time FAVI: 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(93)	Time to sustained symptom resolution: first of two consecutive days without symptoms.		HR: 0.87, 95% CI: 0.52-1.45 Median time FAVI: NA (95%CI: 26, NA) Placebo+SoC: 24 days (95%CI: 21, NA)	
Lou, 2021(95)	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 FAVI: 14 days (IQR: 6-38 days) Control: 15 days (IQR: 6-24 days) RR: 1.11, 95% CI: 0.47-2.60 FAVI: 55.55% SoC: 50.00%
McMahon, 2022(96)	Time to virological cure (two successive swabs negative for SARS-CoV-2 by PCR)	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		

Reference	Parameters	Results		
		Overall severity COVID-19	**Mild severity COVID-19**	**Moderate severity COVID-19**
	Time to symptom resolution (fever, cough, sore throat, fatigue)	Fatigue: Log-rank p = 0.4		
Ruzhentsova, 2021(97)	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(98)	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 FAVI: 6 days Placebo: 7 days
Udwadia, 2021(102)	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 FAVI: 3 days (IQR: 2-4 days) Control: 4 days (IQR: 3-5 days) RR: 0.97, 95% CI: 0.90-1.03 FAVI: 96.55% SoC: 100%	

Abbreviations: FAVI = Favipiravir; Comp = Comparator; SoC = Standard of Care; RR = Relative Risk; CI = Confidence Interval; HR = Hazard Ratio; IQR = Interquartile Range; NA = Not Available.

4.3.6. Safety outcomes

Seventeen studies reported at least one side effect that can be analysed in the meta-analysis (38,80,86–88,90,92,93,95–103) (Appendix 3.3). 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 (Appendix 3.9). 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 (Appendix 3.10). 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%) (Figure 12) (38,80,92,93,97–100,102,103). Since heterogeneity was moderate, we performed a sensitivity analysis excluding a study by Holubar et al. (2021) (93). 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. (Appendix 3.11). 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.

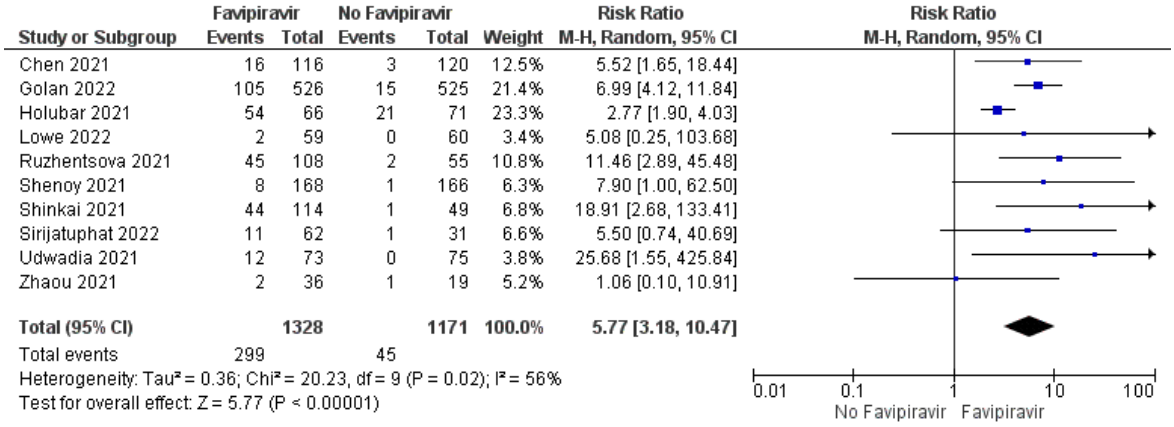

Figure 12. The risk of hyperuricemia is higher in patients treated with favipiravir

4.3.7. Publication bias

The funnel plots for the primary outcome (viral clearance) and the safety outcome (hyperuricemia) were presented in Appendix 3.12a-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 (79). In our analysis, the number of included studies for viral clearance is below ten.

4.4. *Pharmacist's knowledge, perception, and readiness toward Telepharmacy*

4.4.1. Sociodemographic characteristics of the study participants

The sociodemographic characteristics of the study participants are presented in Table 8. The study involved 6,059 pharmacists from healthcare facilities across Indonesia.

Table 8. Descriptive characteristics of study participants (n = 6,059)

Characteristics	***Number***	***%***
Age	6059	
17-25 years	832	13.73%
26-35 years	3662	60.44%
36-45 years	1241	20.48%
>45 years	324	5.35%
Gender		
Male	1132	18.68%
Female	4927	81.32%
Education level		
Pharmacist	5690	93.91%
Master/ Doctoral	369	6.09%
Field of Work		
Community Pharmacy	3217	53.09%
Hospital	1470	24.26%
Public Health Center	1372	22.64%
Internet Access		
Stable	5109	84.32%
Unstable/Poor	950	15.68%
Residence		
Rural	2068	34.13%
Urban	3991	65.87%
Region		
West Region	4753	78.45%
Central Region	1102	18.19%
East Region	204	3.37%

More than half of the pharmacist were aged between 26–35 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%).

4.4.2. 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 (see Table 9). 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 Figure 13. The lowest rate of correct answers (17.97%) was observed for K5 "Counseling via telepharmacy is more expensive."

Table 9. Knowledge and potential determinants of knowledge toward telepharmacy

	Knowledge (N = 6059)							
Variables	**Low**	**%**	**Moderate**	**%**	**High**	**%**	***p-value***	***OR (CI 95%)***
Total Study Population	**9**	**0.15%**	**2519**	**41.57%**	**3531**	**58.28%**		
Age								
17-25 years	1	0.12%	331	39.78%	500	60.10%		ref.
26-35 years	3	0.08%	1555	42.46%	2104	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%	2039	41.38%	2880	58.45%		ref.
Education level								
Pharmacist	9	0.16%	2350	41.29%	3332	58.55%		ref.
Master/ Doctoral	0	0.00%	169	45.92%	199	54.08%	**0.11**	084 (0.68-1.04)
Field of Work								
Community Pharmacy	8	0.25%	1308	40.66%	1901	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%	2117	41.44%	2984	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%	1217	58.85%	0.55	1.03 (0.93-115)
Urban	6	0.15%	1671	41.87%	2314	57.98%		ref.
Region								
West Region	6	0.13%	1982	41.68%	2767	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)

CI = confidence interval. OR = odds ratio. Ref = reference. $p < 0.05$ indicates statistical significance.

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 (see Table 10). Our results indicate that the highest percentage score on perception was achieved on P5 (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?" (Figure 14).

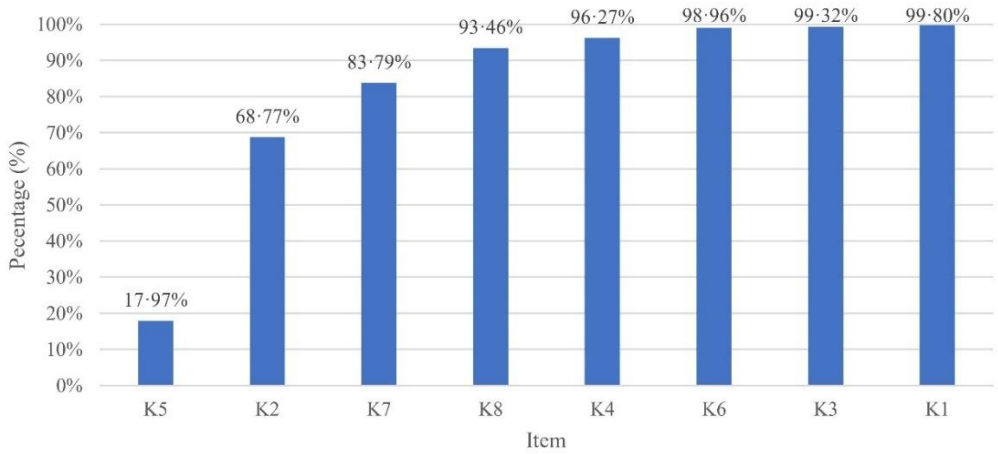

Figure 13. Percentage of correct responses to each knowledge item (K1–K8) regarding telepharmacy (see Appendix 4.2 for item descriptions)

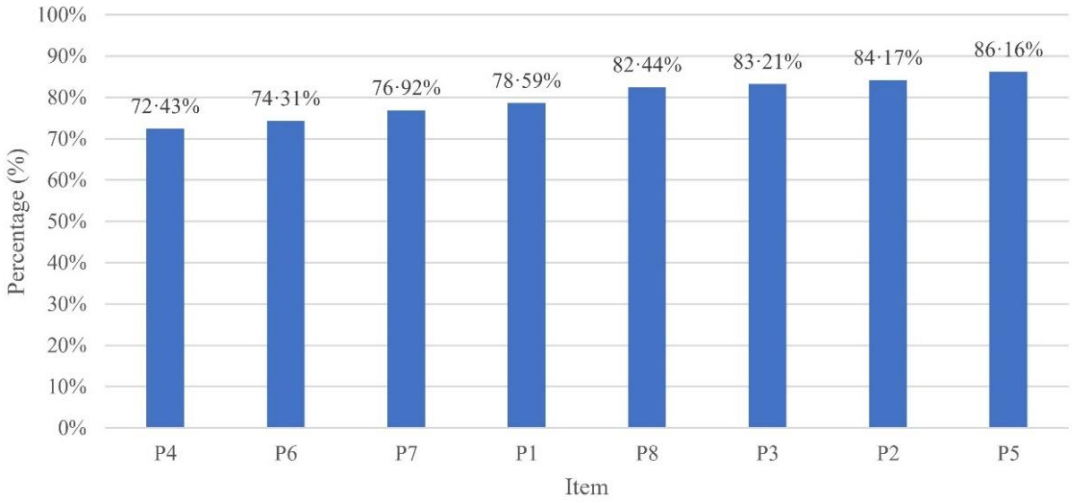

Figure 14. Percentage of "Strongly agree" responses for each perception item (P1–P8) regarding telepharmacy (see Appendix 4.2 for item descriptions)

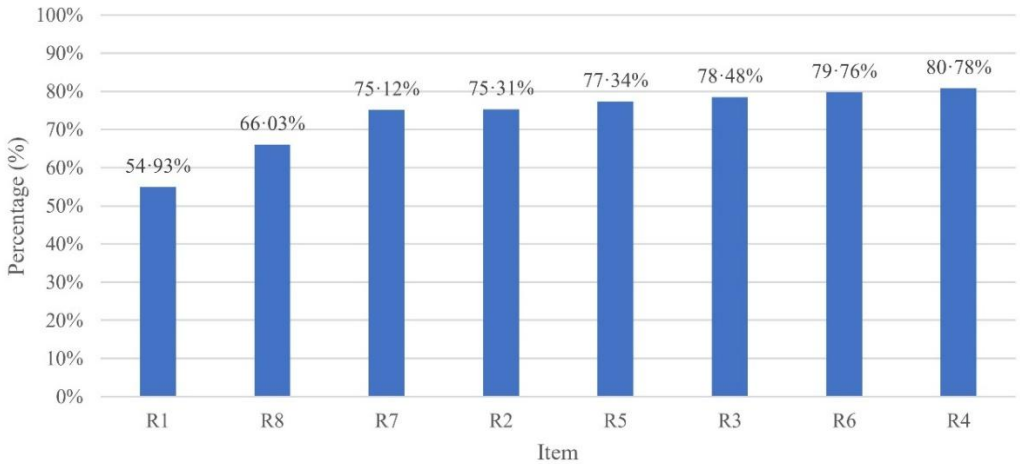

Figure 15. Percentage of "Strongly agree" responses for each readiness item (R1–R8) toward telepharmacy (see Appendix 4.2 for item descriptions)

Table 10. Bivariate analysis of perception and potential determinants of perception toward telepharmacy

	Perception (N = 6059)							
Variables	**Low**	**%**	**Moderate**	**%**	**High**	**%**	***p-value***	***OR (CI 95%)***
Total Study Population	**93**	**1.53%**	**3848**	**63.51%**	**2118**	**34.96%**		
Age								
17-25 years	11	1.32%	540	64.90%	281	33.77%		ref.
26-35 years	58	1.58%	2320	63.35%	1284	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%	3173	64.40%	1679	34.08%		ref.
Education level								
Pharmacist	90	1.58%	3625	63.71%	1975	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%	2017	62.70%	1141	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%	3201	62.65%	1836	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%	1359	65.72%	669	32.35%	**<0.01**	0.83 (0.74-0.93)
Urban	53	1.33%	2489	62.37%	1449	36.31%		ref.
Region								
West Region	73	1.54%	3038	63.92%	1642	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)

CI = confidence interval. OR = odds ratio. Ref = reference. $p < 0.05$ indicates statistical significance.

As shown in Table 11, 24.34%, 70.21%, and 5.45% of participants demonstrated a high, moderate, and low level of readiness for telepharmacy, respectively. According to Figure 15, 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 (54.93%) was obtained for R1 “I am ready to work on telepharmacy projects even in rural areas without an incentive.”

Table 11. Bivariate analysis of readiness and potential determinants of readiness toward telepharmacy

Variables	Readiness (N = 6059)						*p-value*	*OR (CI 95%)*
	Low	**%**	**Moderate**	**%**	**High**	**%**		
Total Study Population	**330**	**5.45%**	**4254**	**70.21%**	**1475**	**24.34%**		
Age								
17-25 years	34	1.29%	579	22.00%	219	26.32%		ref.
26-35 years	200	5.46%	2559	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%	3503	71.10%	1158	23.50%		ref.
Education level								
Pharmacist	316	5.55%	4008	70.44%	1366	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%	2235	69.47%	783	24.34%		ref.
Hospital	61	4.15%	1035	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%	3568	69.84%	1277	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%	1450	70.12%	487	23.55%	**0.08**	0.90 (0.80-1.01)
Urban	199	4.99%	2804	70.26%	988	24.76%		ref.
Region								
West Region	271	5.70%	3379	71.09%	1103	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)

CI = confidence interval. OR = odds ratio. Ref = reference. $p < 0.05$ indicates statistical significance.

Regarding sociodemographic determinants, age, gender, education level, internet access, residence, and region demonstrated p-values < 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 12).

Table 12. Multivariate analysis of independent determinants of knowledge, perception, and readiness toward telepharmacy

Variables	Knowledge		Perception		Readiness	
	p-value	**aOR (95% Cl)**	***p-value***	**aOR (95% Cl)**	***p-value***	**aOR (95% Cl)**
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.		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.

5. DISCUSSION

5.1. *Comparison of outpatient antibiotic use in elderly population of Hungary and Sweden*

This study presented the first age-specific comparison of antibiotic use in elderly populations between Hungary and Sweden, revealing higher antibiotic exposure in Hungarian elderly. Several factors might explain the higher antibiotic exposure in the Hungarian elderlies compared to Swedish.

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 had poorer health status (104). 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 (105). An epidemiological research revealed that patients with diabetes suffer infections more frequently than those without diabetes with consequent higher antibiotic use (106). The prevalence of diabetes in the elderly was higher in 2014 in Hungary than in Sweden (18.6% vs. 12.6%)(107). Obesity has also been an independent risk factor for infections in retrospective and prospective studies (108). It increases the risk of pneumococcal respiratory tract infections (RTI), skin, gastrointestinal tract, and urinary tract infections (UTI) in elderly individuals (109,110). The prevalence of obesity in the elderly was much higher in 2014 in Hungary than in Sweden (26.5% vs. 14.5%) (111).

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%)(112). 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 (113). 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) (114). 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 (115).

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 (116). 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 (117).

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 (118). 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 (119). 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 (120). 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 (121).

Moreover, antibiotic use is influenced by the existence of a national antibiotic policy (122). Sweden implemented the WHO recommendations for antibiotic stewardship in the form of a national strategic program to combat antibiotic resistance (STRAMA), which is a continuously evolving collaboration that has been in place since 1995 (123). In contrast, a national antibiotic policy is not implemented with clear targets, responsibilities, and dedicated funding in Hungary (117). Market forces and manufacturers’ marketing activity can also largely influence prescription practices in Hungary (117). The number of generics is very high in Hungary because they aim to reduce the price as much as possible (124,125), which can promote higher antibiotic use.

Overall, our study revealed that elderly females were prescribed more antibiotics than males in both 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 (126). 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 (126). 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 (117). 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 (127).

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 established in previous research as a drug of choice for respiratory tract infections (RTI) in Hungary (128). Swedish policy recommends prescribing narrow-spectrum penicillin’s in ambulatory care for RTI (129) 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%) (130). 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 (131). 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 (132). 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 (133). Disruption of the human microbiome by antibiotic use can lead to AMR infections and several diseases such as allergies, asthma, obesity or vitamin K deficiency (134).

Quinolones was also more frequently used in Hungary than in Sweden (34.53% vs. 9.98% of total ambulatory use antibiotic use in the elderly, respectively). Previous research showed that fluoroquinolones were commonly used in ambulatory care to treat urinary tract infections and also respiratory tract infections (RTIs) in Hungary (135–137). Contrarily, pivmecillinam and nitrofurantoin were proved to be the first-line antibiotics to treat community-acquired UTIs in Sweden (138). The consequences of high fluoroquinolone use can be various. The Food and Drug Administration has placed a "box warning" on fluoroquinolone antibiotics that older adults are being at an elevated risk of serious side effects, including tendon rupture, delirium, peripheral neuropathy, blood sugar disturbances, and aortic dissection (139). Fluoroquinolones also increase the risk of CDI (*Clostridioides difficile* infection) (18). 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 hypokalemia, hypomagnesaemia might be present more frequently in the elderly, they are more vulnerable to potentially fatal cardiac arrhythmias such as TdP (140). 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 (130).

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 (141). The (un)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 updated the guidelines every three years (142).

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 (143) and linked to an increased prevalence of RTI during the winter months, resulting in higher antibiotic prescription rates during this time (143).

Viral RTI and influenza-like syndromes were the most frequent infections in winter in both countries (144,145); thus, antibiotics were possibly prescribed for self-limiting viral infections in Hungary. The close correlation between viral respiratory infections, such as influenza and antibiotic prescriptions (146), suggests that reducing the incidence of influenza through vaccination efforts in elderly people (147) 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%) (148), which might result in lower influenza illness rates in Sweden.

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 used 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 rate in the two countries.

5.2. *Antibiotic knowledge assessment questionnaire in undergraduate pharmacy students*

To our best knowledge, this was the first study to develop Antibiotic Knowledge Assessment Questionnaire (AKAQ) using the Rasch measurement model as a psychometric analysis. Rasch analysis is different from item response theory (149). It addresses several problems in assessing misconceptions not resolved by classical test theory, such as accurately detecting item difficulty, determining item and person misfits, and identifying Differential Item Functioning (DIF) items(63).

Linacre (67,69) established ideal ranges for infit and outfit mean-square (MNSQ) and z-standardized (ZSTD) scores to minimize the inclusion of misfitting items (questions) and persons. AKAQ was analyzed using Rasch analysis, and the results showed that these questionnaires had a good model fit for the 28 items and 447 persons in the final tool based on the MNSQ and ZSTD scores. However, our findings revealed 56 persons with misfit MNSQ values (see Appendix 2.2), but had positive point measure correlations (PTMEA Corr), indicating that these items measure the same dimension. Items with positive PTMEA (+) values can effectively distinguish respondent abilities (64). We excluded persons with misfit values to enhance the measurement efficiency of the questionnaire (67,150).

The identification and exclusion of misfitting items (questions) and persons (i.e., respondents with response patterns inconsistent with the Rasch model) in the AKAQ were crucial steps in refining the questionnaire. Our decision to exclude specific item were based on rigorous analysis, considering both statistical indicators and practical implications. We found one item misfit (K7) based on outfit MNSQ value. K7 item ("amoxicillin is an antibiotic") has the lowest item difficulty level (see Appendix 2.6) because it has a 99.0% percentage of correct answers. Therefore, this K7 were excluded due to their consistently high correct response rates, indicating a lack of variability among respondents. Retaining such items would not contribute meaningfully to measuring antibiotic knowledge as they failed to differentiate respondents' knowledge levels. This exclusion process was guided by measurement efficiency and construct validity principles. Post-exclusion, the AKAQ demonstrated improved utility and robustness, with reliability tests showing acceptable to high internal consistency according to the National Quality Forum's Measure Evaluation Criteria (151).

The AKAQ achieved unidimensionality criteria, confirming that all items measure a one-dimension, including general knowledge of antibiotic, antimicrobial resistance (AMR) and antimicrobial stewardship (AMS). All unidimensionality parameters confirming the construct validity of the AKAQ achieved an acceptable threshold (67,69,152).

The item-person analysis indicated that all items could measure students' antibiotic-related knowledge across a proficiency spectrum. The Wright maps' construction, from easiest to hardest items, facilitated an effective evaluation of student abilities (67,69). The item about the "ability of beta-lactamase enzyme to destroy the beta-lactam ring" was the most difficult item to answer by pharmacy students, and similar findings have been reported by previous studies from the United Kingdom(55) and Pakistan(24). The antibiotic resistance mechanism-related question was difficult for pharmacy students to adequately answer, probably because of the inadequate education in the pharmacy curriculum, especially for students at the earlier semesters (first to fifth semesters) than at the later semesters (sixth to twelfth semesters). The easiest item in the AKAQ (after exclusion of 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(55), and Sri Lanka(153), where the item related basic knowledge of antibiotic efficacy in treating bacterial infection was also correctly answered by >95% of pharmacy students.

Furthermore, the DIF analysis revealed that only two of the 28 items were biased based on semesters. DIF items were found only in K6 and K19 because these items were easier for students in the later semesters (6^{th}–12^{th}) compared to those in the earlier semesters (1^{st}–5^{th}). This pattern is supported by research from China (154) support these findings that later semesters (6^{th}–12^{th}) students had more knowledge than students in the earlier semesters (1^{st}–5^{th}). This may be due to their updated knowledge of pharmacology (including antibiotics courses) which they have completed more recent exposure. However, these items were still retained to analyze 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. By meticulously examining MNSQ and ZSTD values, Rasch analysis identifies and excludes misfitting items and respondents, ensuring the questionnaire's validity and precision. Guided by Linacre's criteria, this process yields a tool with strong fit validity and high internal consistency, meeting the National Quality Forum's standards. The confirmation of unidimensionality further validates that all items measure antibiotic knowledge effectively. Our study demonstrates the AKAQ's ability to assess a wide range of antibiotic-related knowledge among students, making it a robust and impactful tool for global educational contexts.

This study has some limitations. The diversity of pharmacy education in Indonesia, with no standardized curriculum, may introduce bias affecting external validity. The AKAQ focuses on basic antibiotic knowledge, making it relevant for students in early curricula stages. However, caution is needed when applying these findings to other educational contexts. Data were self-reported by volunteers recruited via WhatsApp, which may introduce selection bias. The sample's concentration from certain universities could also impact external validity. Further studies should validate the questionnaire across diverse global student populations and educational levels. Additionally, future DIF analysis should compare gender differences.

5.3. *Favipiravir in treatment of mild to moderate COVID-19: A meta-analysis*

Favipiravir had been used in many countries to treat COVID-19 infections shortly after the outbreak of the pandemic. 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 (37,38). The results of these trials have been summarized in meta-analyses (155,156). 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 the need for respiratory support (including 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) (156).

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 (157).

Our meta-analysis was the first meta-analysis of randomized controlled trials that assessed 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 this meta-analysis is that it was based only on the results of randomized controlled trials (RCTs). The 20 included RCTs were carried out by independent research groups in different countries in Europe, America, Asia, and Australia. However, our study had 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 2020-2022, 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 had 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 was often incompletely reported, making it difficult to evaluate the efficacy of favipiravir across different age groups. Fifth, although it is known that favipiravir is more effective in the first phase of the disease, in some trial's 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.

5.4. *Pharmacist's knowledge, perception, and readiness toward Telepharmacy*

Our results indicated that more than half (58.28%) of respondents had a high knowledge level about telepharmacy. This result is similar to a study conducted in Malaysia, in which 67% of the participants had a high level of knowledge.(44) 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.(158) This variance might be due to differences in the study population and the time of the study, as our survey was conducted in 2023, while the Saudi Arabian study was conducted earlier in 2022, possibly reflecting different stages of telepharmacy infrastructure development and public awareness. It has been reported that the success of telepharmacy services depends largely on the level of technological infrastructure, such as efficient Internet connection.(49)

Pharmacists are in charge of providing pharmaceutical care to patients, who may not have direct contact with them (i.e., through telecommunication).(12) 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 USA 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.(159)

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 COVID pandemic, to facilitate the provision of instructions on the use of medication and teach back method, where patients are asked to repeat instructions to confirm their understanding.(160–162) However, a cross-sectional study from the Netherlands reported that video communication was rarely used for the provision of pharmaceutical care services via telepharmacy during the pandemic.(163)

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.(164) Strikingly different from our findings, 91% of participants in a study conducted in Malaysia considered that employing a telepharmacy system could reduce travel and waiting time for patients and be a cost-effective option for patients.(44) The above difference may be explained by the lack of telepharmacy implementation in Indonesia, which limits the awareness of pharmacists regarding certain telepharmacy-related aspects. Moreover, counseling services in traditional pharmacy remain free of charge in Indonesia, especially for patients covered by the 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 pharmacistreported a positive perception of telepharmacy. This finding is comparable to those of studies conducted in Malaysia(44) and Jordan.(10) 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.(165) This difference may be attributed to different methods utilized 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.(44,49,166)

Most participants agreed that telepharmacy would improve access to healthcare 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(49,50). 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 (167,168).

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 United States Department of Veterans Affairs integrated a healthcare system for patients who required anticoagulation management services in a community outpatient clinic. The results showed that the rate of achievement of the international normalized ratio (INR) remained stable between previous face-to-face management and clinical video telepharmacy, with higher levels of patient satisfaction observed with the latter approach(169).

In addition, 94.55% (Moderate= 70.21%; High= 24.34%) of the participants had a moderate-to-high level of readiness, higher than a previous study conducted in Malaysia (68%) (44) and Saudi Arabia (<40%) (158). Most respondents in our study were willing to engage in telepharmacy-related training and activities, but expressed concerns about the lack of incentives and the potential increase in workload. These concerns align with previous reports identifying workload, reimbursement, and lack of incentives as key barriers to telepharmacy (44,49). Therefore, addressing provider workload and offering appropriate compensation are essential for developing a sustainable telepharmacy system.

In our study, several sociodemographic factors were identified as predictors of perception and readiness toward telepharmacy among Indonesian pharmacists. Specifically, male gender, stable internet access, and residence in the central region of Indonesia were positively associated with better perception scores. However, these factors were not significantly associated with knowledge levels. 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 (170). 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 (165). 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 (10).

In our study, younger age, male gender, postgraduate education, stable internet access, and residing in the central region of Indonesia were correlated with higher levels of readiness toward telepharmacy. A study conducted in Saudi Arabia, focused on KPR for telepharmacy amongspecialized 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.(158) 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 (171).

This study has some limitations. Selection bias may have occurred due to the distribution of the online survey through WhatsApp groups of registered pharmacists in Indonesia. Pharmacists might also hesitate to provide honest responses that could harm their professional image, although confidentiality assurances likely mitigated this bias. Despite these limitations, the study offers valuable insights into pharmacists' perceptions and readiness for telepharmacy. It is also strengthened by including participants from all provinces of Indonesia.

6. SUMMARY AND CONCLUSION

This thesis provides significant insights into cross-national drug utilization patterns, pharmacy education among Indonesian undergraduate pharmacy students, clinical evidence through meta-analysis, and digital healthcare innovation across multiple countries and contexts.

First, the comparative analysis (cross national comparison- CNC) of the scale and pattern of elderly ambulatory antibiotic use revealed differences 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.

Second, the successful development and validation of the Antibiotic Knowledge Assessment Questionnaire (AKAQ) for undergraduate pharmacy students in Indonesia mark a significant advancement. The AKAQ achieved adequate fit validity and reliability criteria using the Rasch analysis, affirming its psychometric robustness. 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 various educational levels.

Third, the evaluation of Favipiravir for COVID-19 treatment showed that it 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. These results suggest the use of favipiravir as a routine therapy that should be initialized after the diagnosis of COVID-19 is questionable.

Lastly, the study on Indonesian pharmacists' perspectives on telepharmacy revealed high levels of knowledge but moderate perceptions and readiness, influenced by various sociodemographic factors. Gender, internet access, and region of residence were identified as independent determinants of perception, while age, gender, Internet access, education level, and region of residence were significantly associated with readiness. These findings can inform health authorities in Indonesia in developing and implementing effective telepharmacy policies.

In conclusion, this thesis underscores the importance of a) cross-national comparative studies on antibiotic use, b) evidence based synthesis of the results of available randomized controlled trials c) robust psychometric tools, and d) comprehensive assessments of healthcare innovations. The insights gained can contribute to improved healthcare policies and practices,in antimicrobial use (including both antibiotic and antiviral agents), pharmacy education, and telepharmacy. Further research and targeted interventions are essential to continue advancing these areas and enhancing global health outcomes.

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APPENDIX

Appendix-Study II: Antibiotic knowledge assessment questionnaire in undergraduate pharmacy students

Appendix 2.1

Content Validity Index (CVI) of the 29-items draft Antibiotic Knowledge Assessment Questionnaire (AKAQ) from 4 experts

Variable	Panel 1		Panel 2		Panel 3		Panel 4		Expert in Agreements	I-CVI Score	S-CVI Score
Construct	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 2.2 Knowledge Items & Correct Percentages

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 2.3 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

Appendix 2.3 Person Fit Measurement

No	COUNT	SCORE	INFIT MNSQ	INFIT ZSTD	OUTFIT MNSQ	OUTFIT ZSTD	PTMA	RMSR
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
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

Appendix 2.3 Person Fit Measurement

No	COUNT	SCORE	INFIT MNSQ	INFIT ZSTD	OUTFIT MNSQ	OUTFIT ZSTD	PTMA	RMSR
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
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

Appendix 2.3 Person Fit Measurement

No	COUNT	SCORE	INFIT MNSQ	INFIT ZSTD	OUTFIT MNSQ	OUTFIT ZSTD	PTMA	RMSR
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

Appendix 2.3 Person Fit Measurement

No	COUNT	SCORE	INFIT MNSQ	INFIT ZSTD	OUTFIT MNSQ	OUTFIT ZSTD	PTMA	RMSR
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
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

Appendix 2.3 Person Fit Measurement

No	COUNT	SCORE	INFIT MNSQ	INFIT ZSTD	OUTFIT MNSQ	OUTFIT ZSTD	PTMA	RMSR
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
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

Appendix 2.3 Person Fit Measurement

No	COUNT	SCORE	INFIT MNSQ	INFIT ZSTD	OUTFIT MNSQ	OUTFIT ZSTD	PTMA	RMSR
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

Appendix 2.3 Person Fit Measurement

No	COUNT	SCORE	INFIT MNSQ	INFIT ZSTD	OUTFIT MNSQ	OUTFIT ZSTD	PTMA	RMSR
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
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

Appendix 2.3 Person Fit Measurement

No	COUNT	SCORE	INFIT MNSQ	INFIT ZSTD	OUTFIT MNSQ	OUTFIT ZSTD	PTMA	RMSR
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
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

Appendix 2.3 Person Fit Measurement

No	COUNT	SCORE	INFIT MNSQ	INFIT ZSTD	OUTFIT MNSQ	OUTFIT ZSTD	PTMA	RMSR
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

Appendix 2.3 Person Fit Measurement

No	COUNT	SCORE	INFIT MNSQ	INFIT ZSTD	OUTFIT MNSQ	OUTFIT ZSTD	PTMA	RMSR
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
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

Appendix 2.3 Person Fit Measurement

No	COUNT	SCORE	INFIT MNSQ	INFIT ZSTD	OUTFIT MNSQ	OUTFIT ZSTD	PTMA	RMSR
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

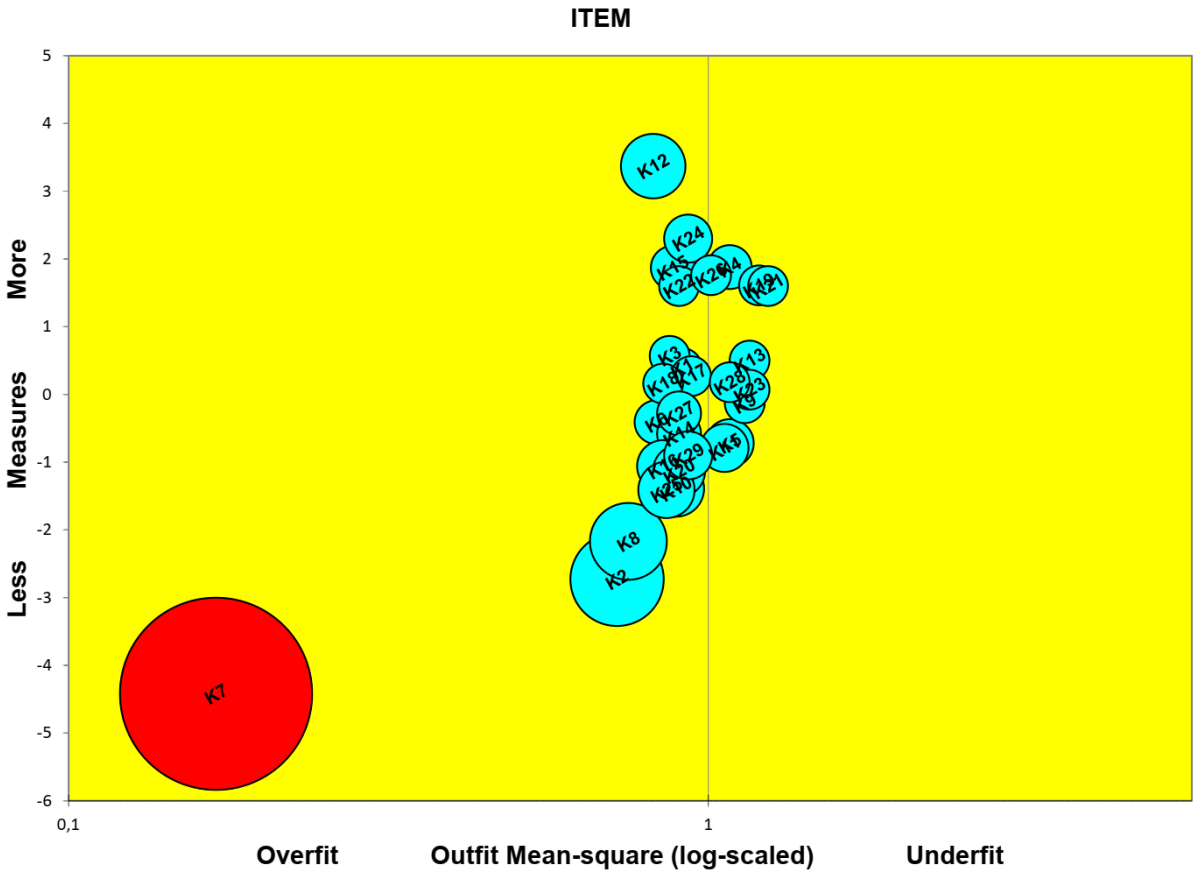
*MNSQ, mean-square; ZSTD, z-standard; PTMA, point measure correlation; RMSR, root-mean-square residual

Appendix 2.4 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 2.5 Item Fit Order (including item K7)



Appendix 2.6 Differential Item Functioning (DIF) by Semester

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;

Appendix-Study III: Favipiravir in treatment of mild to moderate COVID-19: A meta-analysis

Appendix 3.1. Searching strategy

PubMed

(("COVID-19"[Mesh] OR "SARS-CoV-2"[Mesh] OR "COVID-19 drug treatment" [Supplementary Concept]) OR ((((((((((((((((((COVID-19[Title/Abstract]) OR (2019- nCOV[Title/Abstract])) OR ("2019 novel coronavirus disease"[Title/Abstract])) OR ("coronavirus disease 2019"[Title/Abstract])) OR ("COVID-19 pandemic"[Title/Abstract])) OR ("coronavirus disease-19"[Title/Abstract])) OR ("coronavirus disease (COVID)-19"[Title/Abstract])) OR (SARS-CoV-2[Title/Abstract])) OR ("SARS-CoV-2 infection"[Title/Abstract])) OR ("Sars-CoV-2 virus infection"[Title/Abstract])) OR ("novel SARS coronavirus"[Title/Abstract])) OR ("severe acute respiratory syndrome coronavirus 2"[Title/Abstract])) OR ("severe acute respiratory syndrome coronavirus-2"[Title/Abstract])) OR ("Covid-19 treatment"[Title/Abstract])) OR ("treatment of COVID-19"[Title/Abstract])) OR ("management of covid-19"[Title/Abstract])) OR ("treatment of Covid-19 virus infection"[Title/Abstract]))))

AND

(("favipiravir" [Supplementary Concept]) OR ((((((favipiravir[Title/Abstract]) OR ("6-fluoro-3-hydroxy-2-pyrazinecarboxamide"[Title/Abstract])) OR ("T-705"[Title/Abstract])) OR (avigan[Title/Abstract])) OR (avifavir)) OR (favilavir)))

Embase

('coronavirus disease 2019'/exp OR 'severe acute respiratory syndrome coronavirus 2'/exp OR 'covid 19':ti,ab,kw OR '2019- ncov':ti,ab,kw OR '2019 novel coronavirus disease':ti,ab,kw OR 'coronavirus disease 2019':ti,ab,kw OR 'covid-19 pandemic':ti,ab,kw OR 'coronavirus disease-19':ti,ab,kw OR 'coronavirus disease (covid)-19':ti,ab,kw OR 'sars-cov-2':ti,ab,kw OR 'sars-cov-2 infection':ti,ab,kw OR 'sars-cov-2 virus infection':ti,ab,kw OR 'novel sars coronavirus':ti,ab,kw OR 'severe acute respiratory syndrome coronavirus 2':ti,ab,kw OR 'severe acute respiratory syndrome coronavirus-2':ti,ab,kw)

AND

('favipiravir'/exp OR favipiravir:ti,ab,kw OR '6-fluoro-3-hydroxy-2-pyrazinecarboxamide':ti,ab,kw OR 't-705':ti,ab,kw OR avigan:ti,ab,kw OR avifavir:ti,ab,kw OR favilavir:ti,ab,kw)

WoS

TS=(COVID-19 OR 2019-nCOV OR “2019 novel coronavirus disease” OR "coronavirus disease 2019" OR "COVID-19 pandemic" OR "coronavirus disease-19" OR "coronavirus disease (COVID)-19" OR SARS-CoV-2 OR "SARS-CoV-2 infection" OR "Sars-CoV-2 virus infection" OR "novel SARS coronavirus" OR "severe acute respiratory syndrome coronavirus 2" OR "severe acute respiratory syndrome coronavirus-2")

AND

TS=(favipiravir OR "6-fluoro-3-hydroxy-2-pyrazinecarboxamide" OR "T-705" OR avigan OR avifavir OR favilavir)

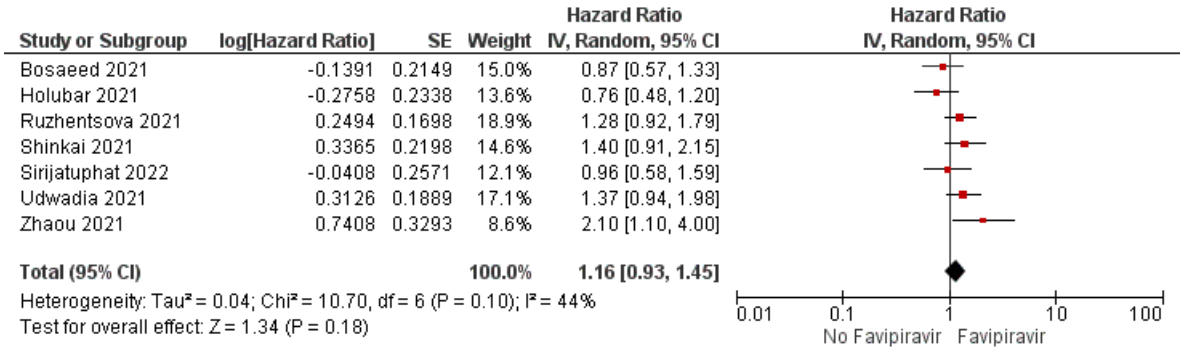
Cochrane

MeSH descriptor: [COVID-19] explode all trees OR MeSH descriptor: [SARS-CoV-2] explode all trees OR ("2019-nCOV" OR "COVID-19" OR “2019 novel coronavirus disease” OR "coronavirus disease 2019" OR "COVID-19 pandemic" OR "coronavirus disease-19" OR "coronavirus disease (COVID)-19" OR "SARS-CoV-2" OR "SARS-CoV-2 infection" OR "Sars-CoV-2 virus infection" OR "novel SARS coronavirus" OR "severe acute respiratory syndrome coronavirus 2" OR "severe acute respiratory syndrome coronavirus-2"):ti,ab,kw

AND

(favipiravir OR "6-fluoro-3-hydroxy-2-pyrazinecarboxamide" OR "T-705" OR avigan OR avifavir OR favilavir):ti,ab,kw

Appendix 3.2 Sensitivity analysis without Lowe et al.: Favipiravir and viral clearance



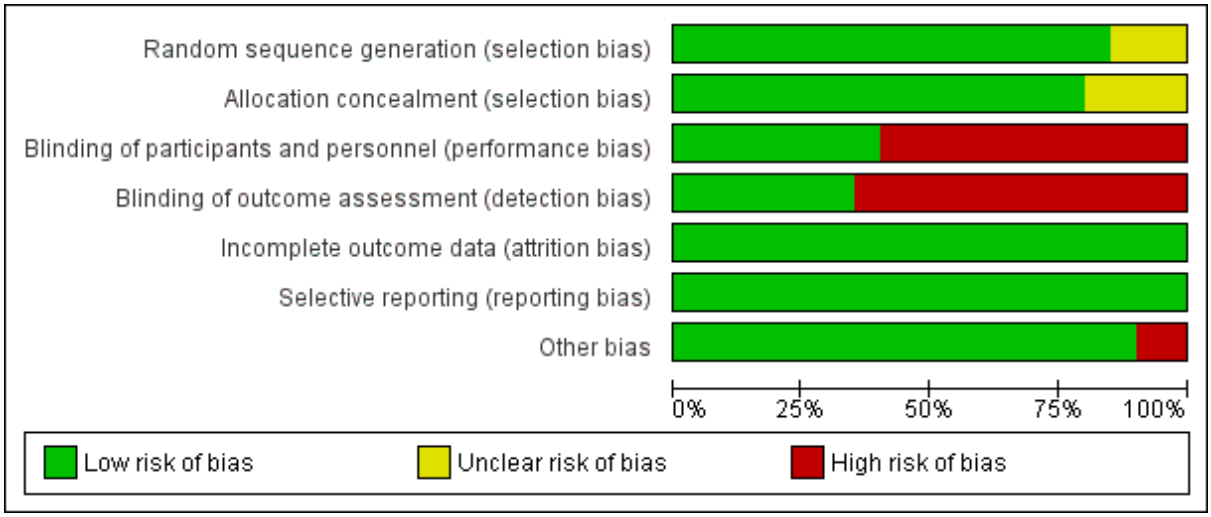
Appendix 3.3 Summary of outcomes for each study

Ref.	Primary Outcomes		Secondary outcomes	Safety outcomes
	Viral Clearance	Clinical Improvement		
Abdur Rahman, 2022[42]	RR		chest imaging improvement	diarrhea, nausea, vomiting
AlQahtani, 2022[37]	RR	RR	mortality, ICU admissions	increased ALT, headache
Balykova, 2020a[38]	RR	RR	mortality	hyperglycemia, increased ALT, increased AST, increased creatine phosphokinase, skin rash
Balykova, 2020b[39]	RR	RR	mortality, hospital discharge	
Bossaed, 2021[30]	HR, RR	HR	mortality, emergency department visits, hospitalizations, ICU admissions	increased ALT, increased AST, increased bilirubin, abdominal pain, diarrhea, dyspnea, headache, nausea, skin rash, vomiting
Chen, 2021[4]		RR	mortality	hyperuricemia, dyspnea
Chuah, 2022[45]		RR	chest imaging improvement, mortality, ICU admissions	
Golan, 2022[43]	RR	Median time, RR	mortality	increased ALT, abdominal pain, constipation, diarrhea, dizziness, dyspnea, myalgia, nasal congestion, nausea, rhinorrhoea, vomiting, hyperuricemia
Holubar, 2021[31]	HR, RR	HR	mortality, emergency department visits, hospitalizations	hyperuricemia, dizziness, nausea
Ivashchenko, 2020[40]	RR		chest imaging improvement, mortality, ICU admissions, hospital discharge	
Lou, 2021[41]	RR	RR	mortality, ICU admissions	decreased haemoglobin, increased ALT, increased AST, increased bilirubin, increased creatine phosphokinase, increased triglyceride, diarrhea, nausea, skin rash, leukopenia
Lowe, 2022[28]	HR, RR		mortality, hospitalizations, ICU admissions	hyperuricemia, increased ALT, increased AST, abdominal pain, anorexia, diarrhea, dizziness, dyspnea, headache, myalgia, nausea, vomiting, nasal congestion
McMahon, 2022[47]		Time to virological cure	mortality, hospitalizations,	diarrhea, dyspnea, nausea, rhinorrhoea, vomiting
Ruzhentsova, 2021[32]	HR	HR, RR	chest imaging improvement, hospitalizations, ICU admissions	hyperuricemia, decreased haemoglobin, hyperglycemia, increased ALT, increased AST, increased bilirubin, increased creatine phosphokinase, abdominal pain, diarrhea, nausea, skin rash
Shenoy, 2021[46]		HR	hospital discharge	hyperuricemia, decreased haemoglobin, increased ALT, increased triglyceride
Shinkai, 2021[33]	HR, RR	HR, RR	chest imaging improvement, mortality	hyperuricemia, increased ALT

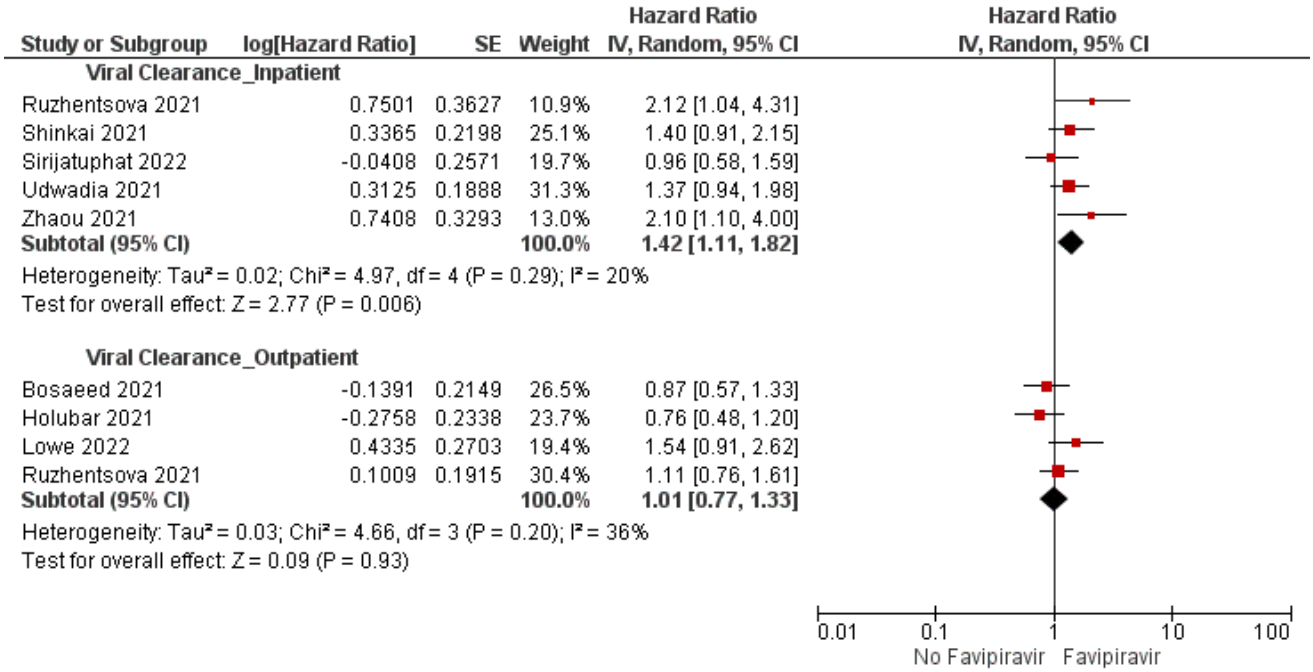
Appendix 3.3 Summary of outcomes for each study

Ref.	Primary Outcomes		Secondary outcomes	Safety outcomes
	Viral Clearance	Clinical Improvement		
Sirijatuphat, 2022[36]	HR	HR, RR	mortality	decreased haemoglobin, hyperglycemia, increased ALT, increased creatine phosphokinase, increased triglyceride, leukopenia, constipation, diarrhea, dizziness, dyspepsia, skin rash, hyperuricemia
Tehrani, 2022[44]		Proportion of patients with normal respiratory rate	hospitalizations	anorexia, dyspnea, myalgia,
Udwadia, 2021[34]	HR, RR	HR, RR	mortality, hospital discharge	hyperuricemia
Zhao, 2021[35]	HR, RR		mortality	hyperuricemia, increased ALT, increased AST, diarrhea, nausea

Appendix 3.4 Risk of bias graph

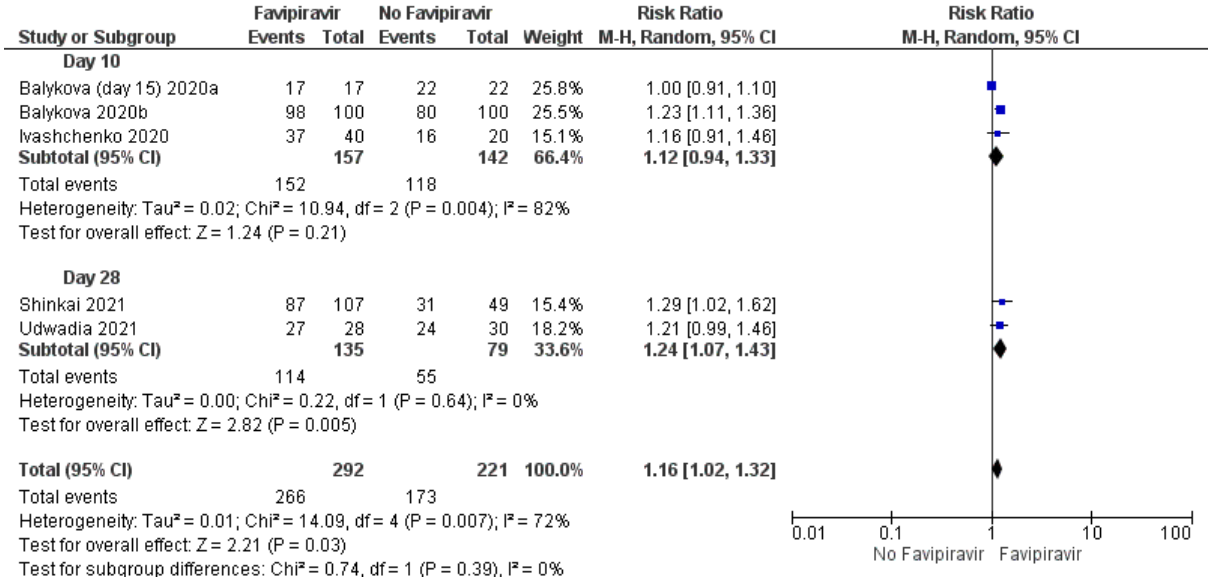


Appendix 3.5. Favipiravir Effectiveness in Inpatients vs. Outpatients

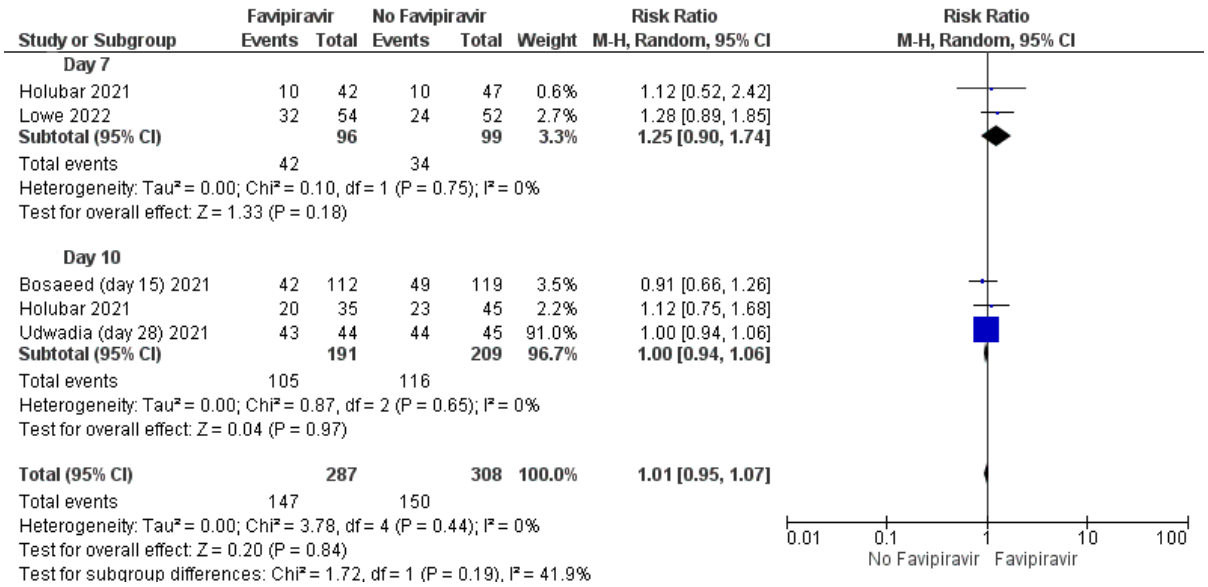


Appendix 3.6. Forest plots for viral clearence subgroup by severity

a. moderate

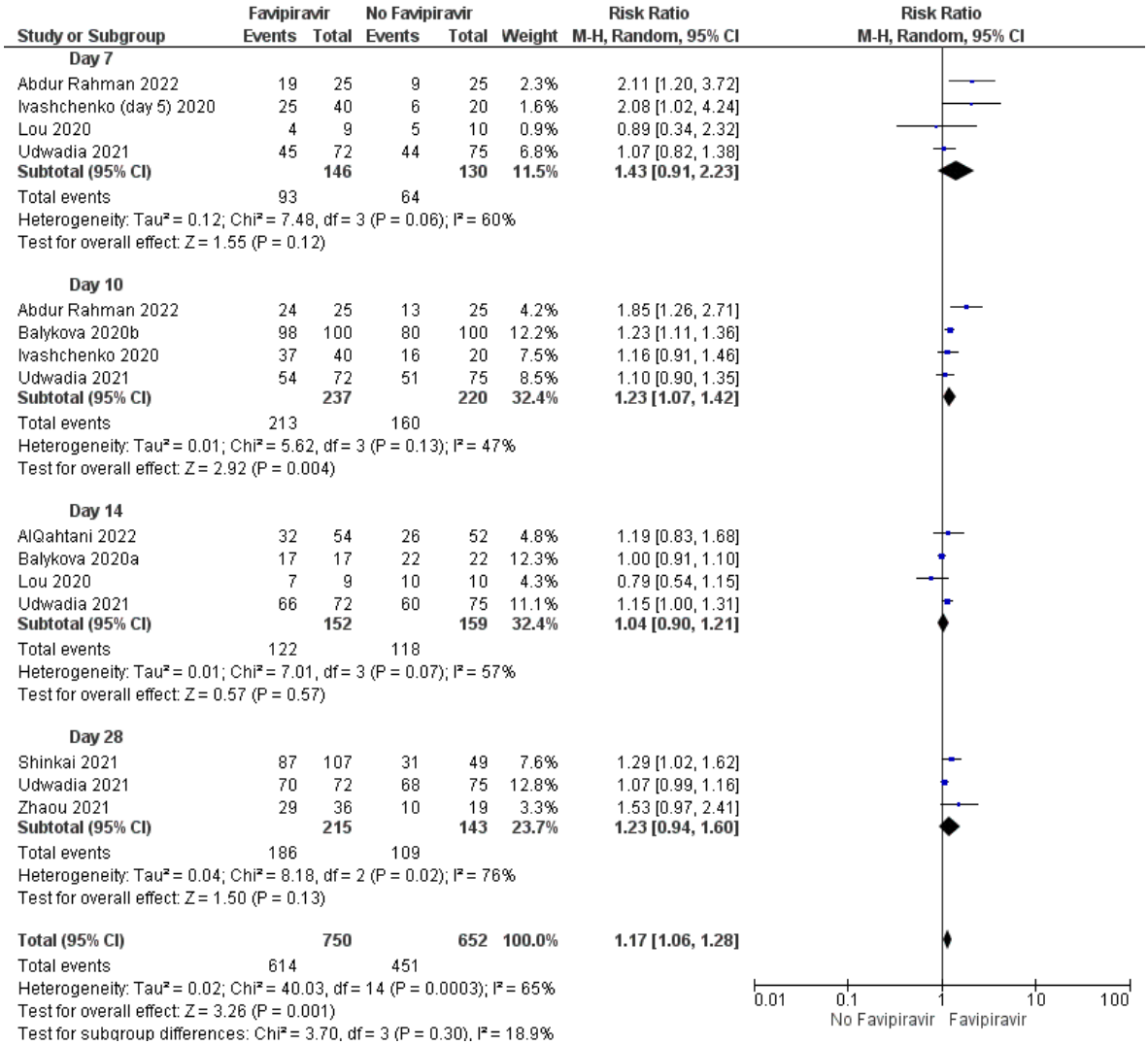


b. mild

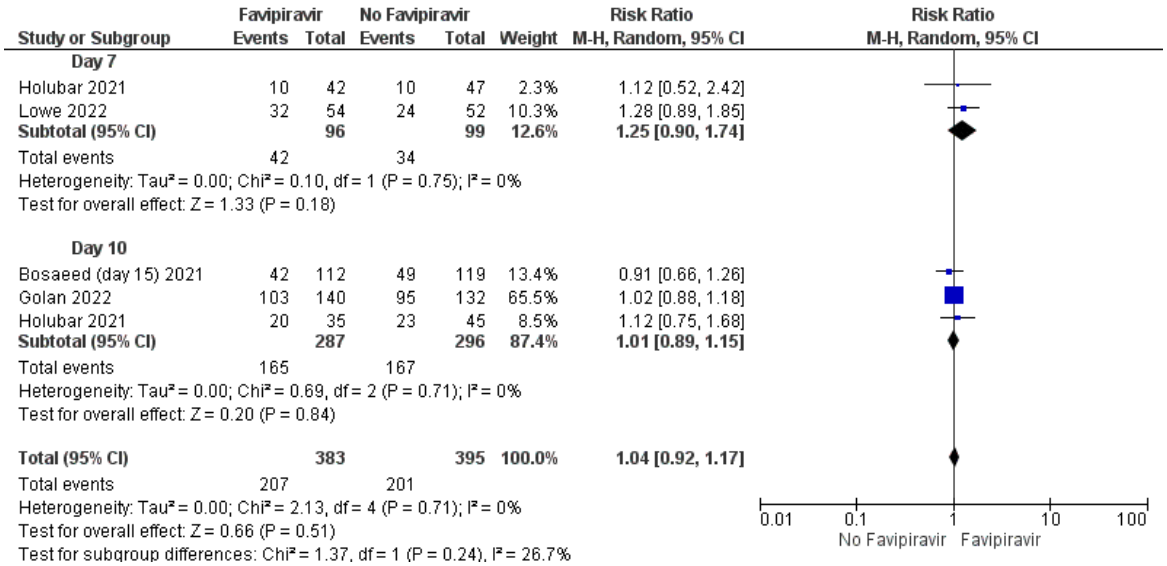


Appendix 3.7 Forest plots for viral clearence subgroup by setting of care

a. hospital care

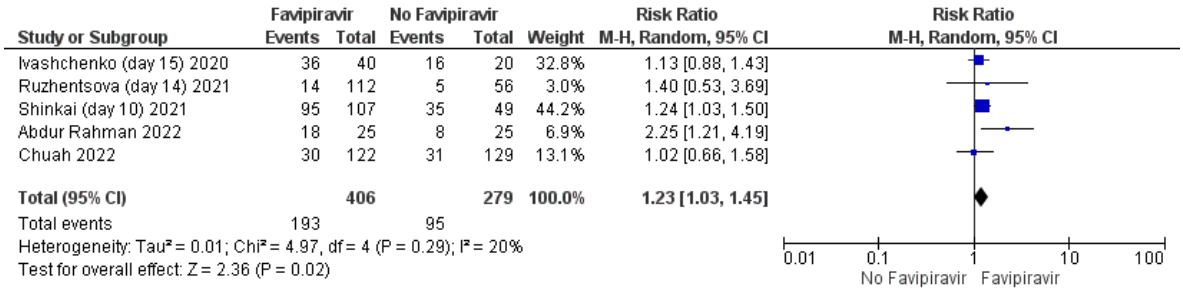


b. ambulatory care

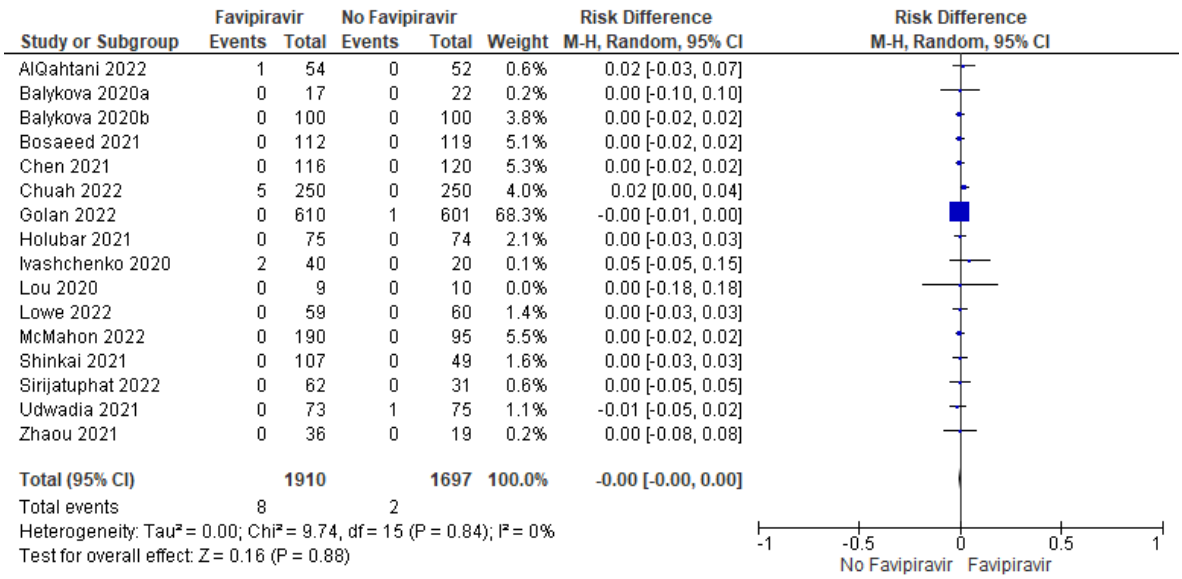


Appendix 3.8 Forest plots for secondary clinical outcomes

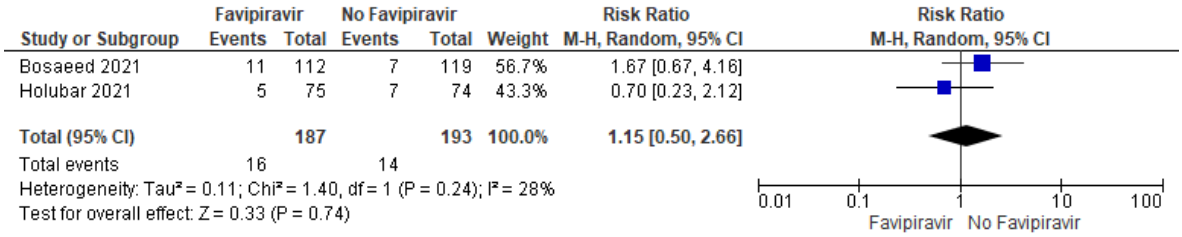
a. chest imaging improvement



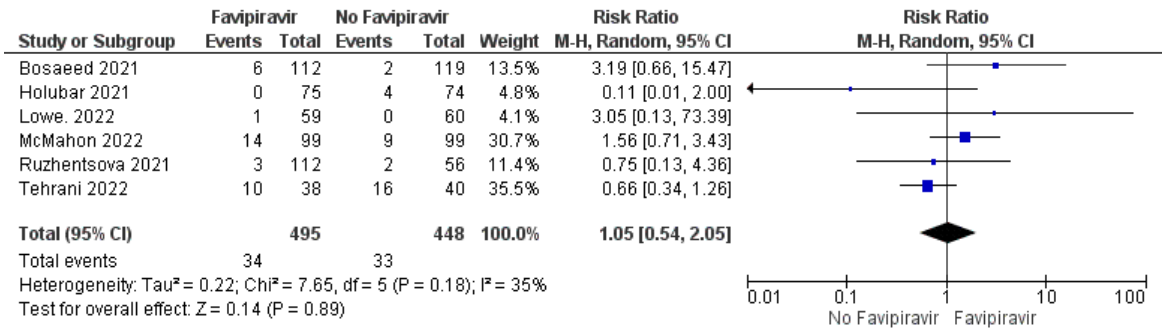
b. mortality



c. emergency department visits

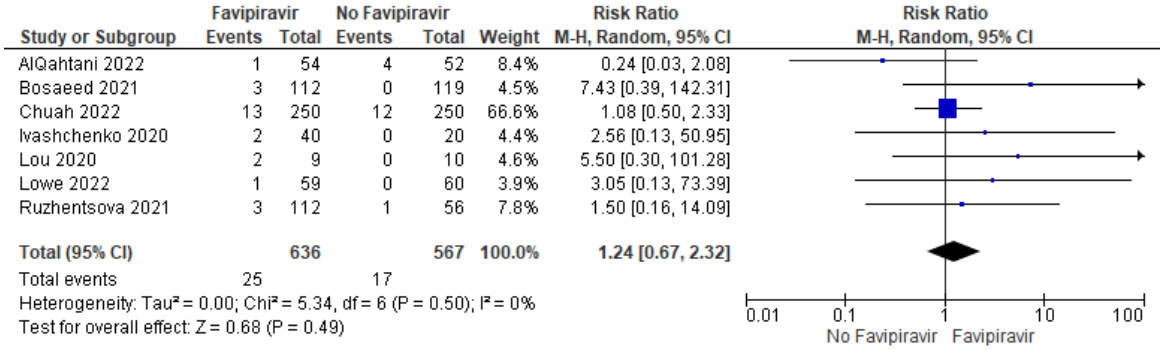


d. hospitalizations

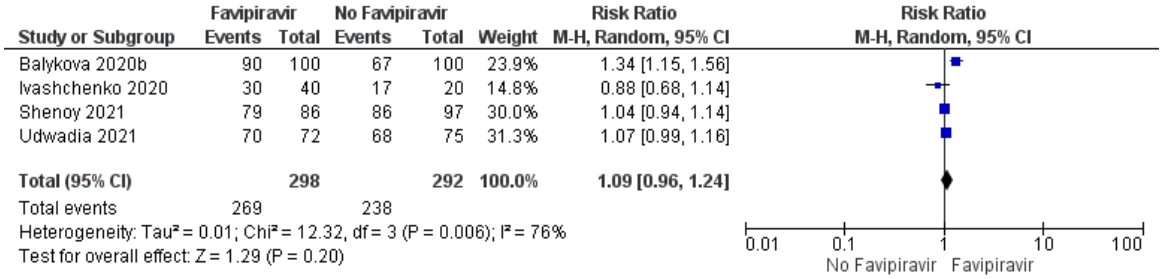


Appendix 3.8 Forest plots for secondary clinical outcomes

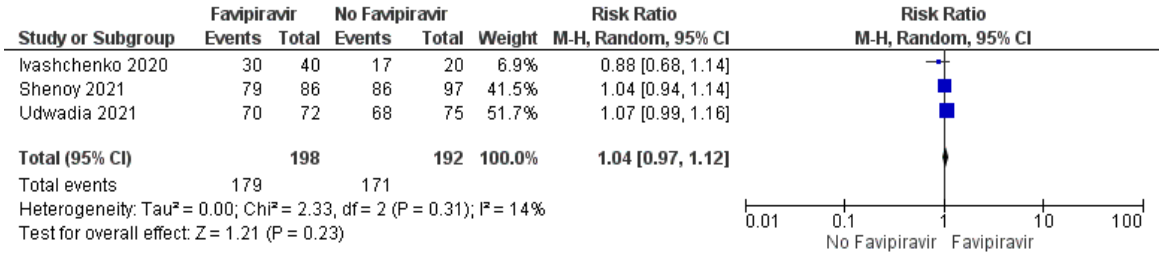
e. ICU admissions



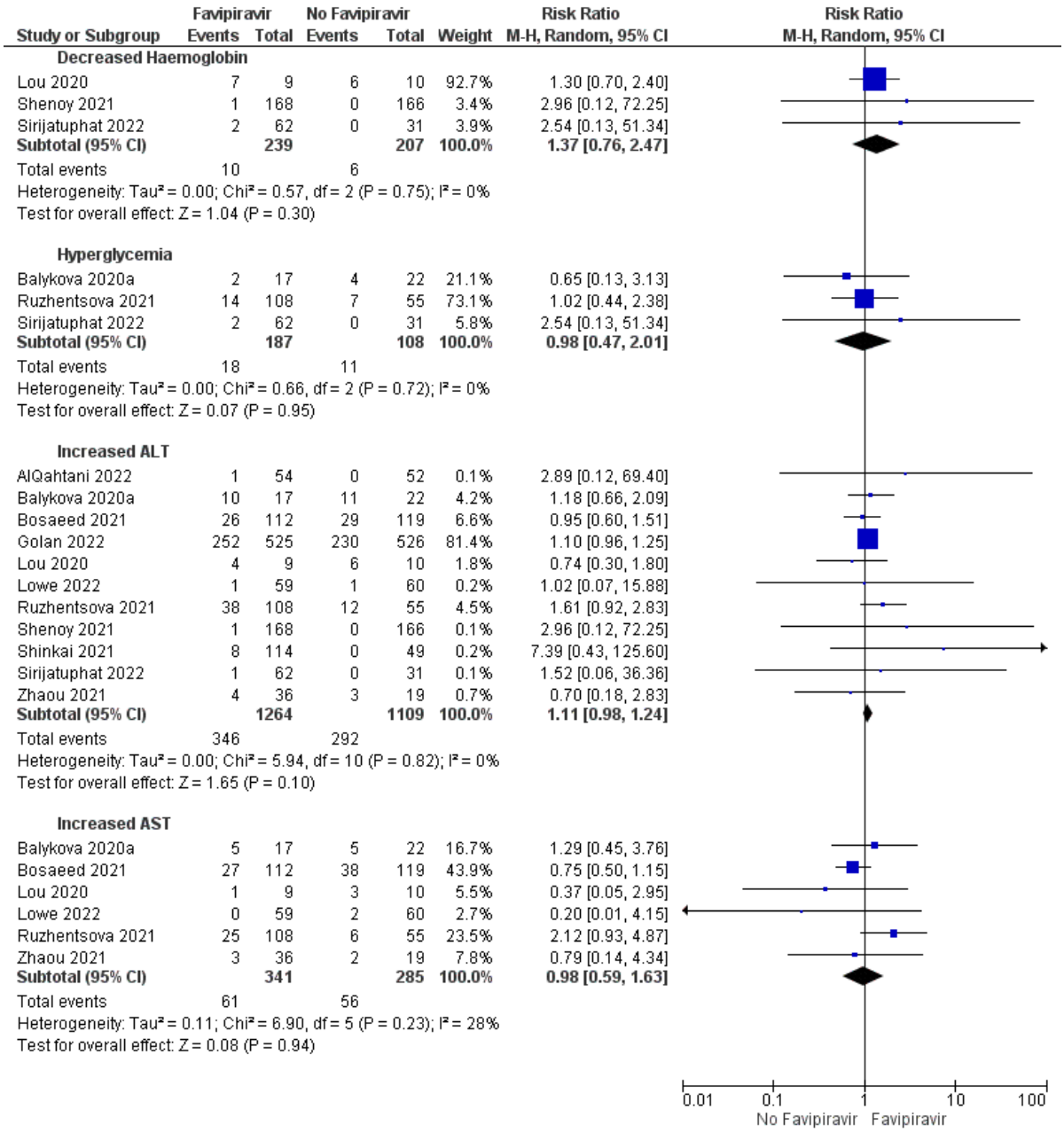
f. hospital discharge



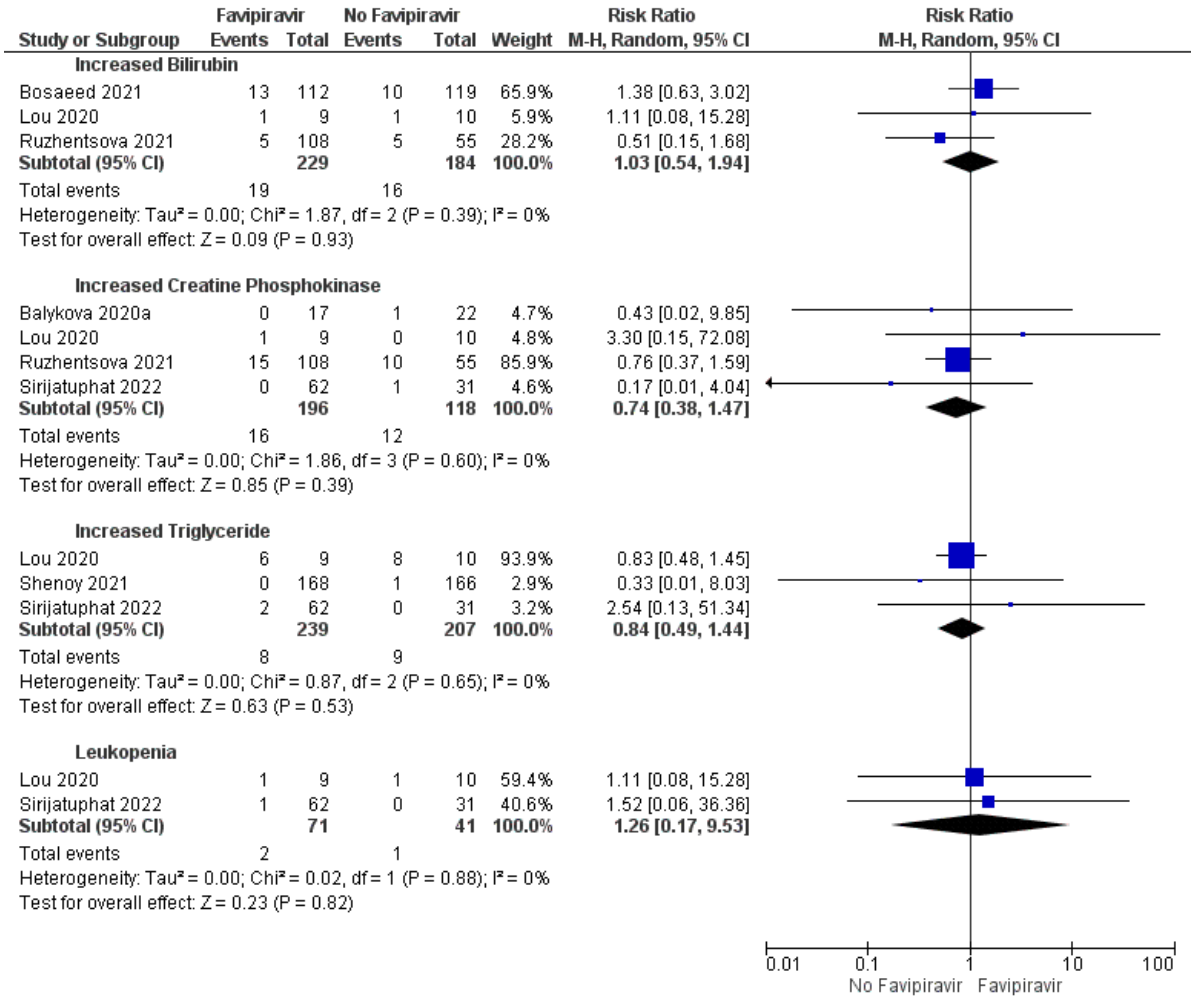
g. sensitivity analysis for hospital discharge



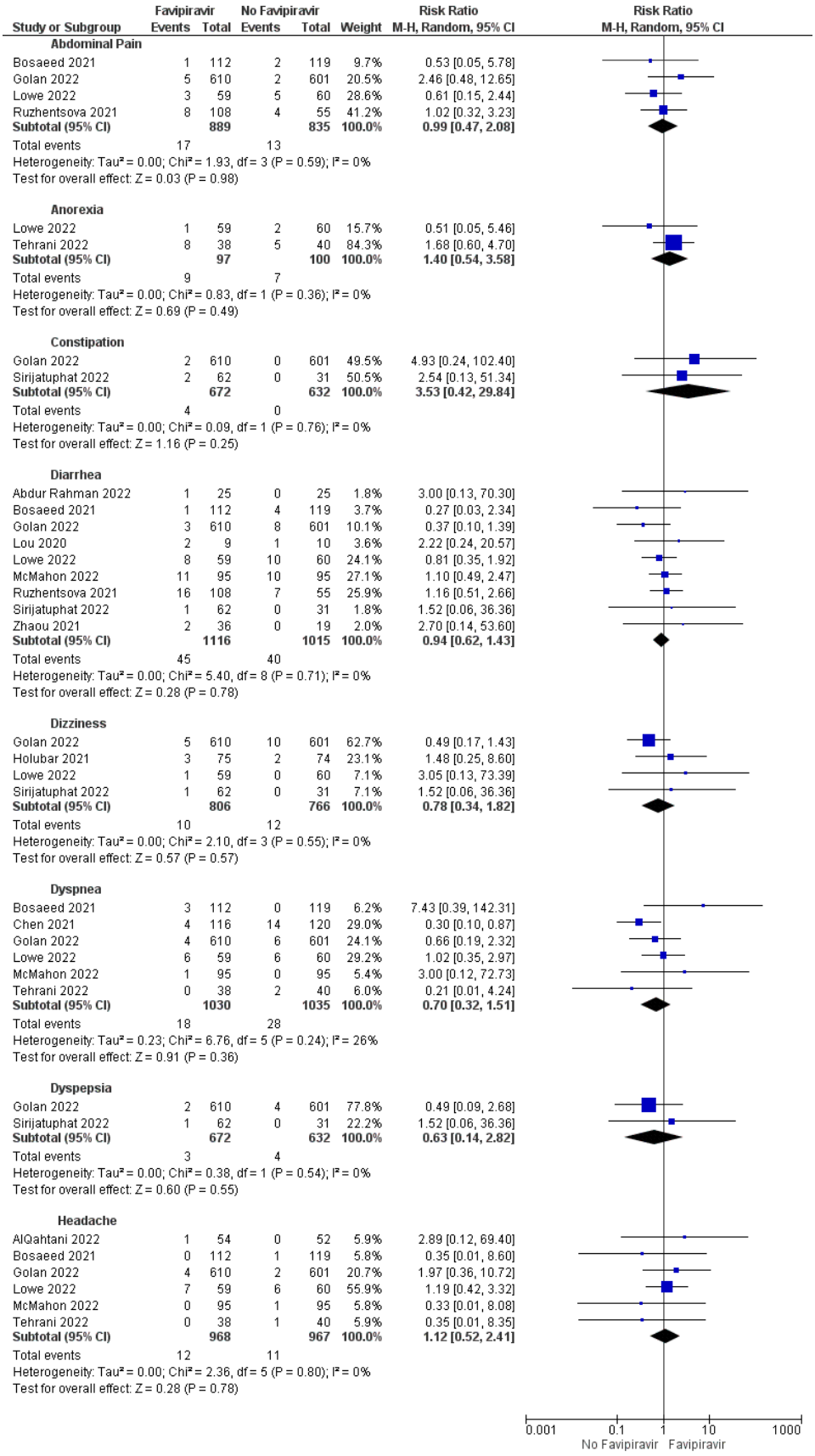
Appendix 3.9 Forest plots for safety outcomes: blood related parameters



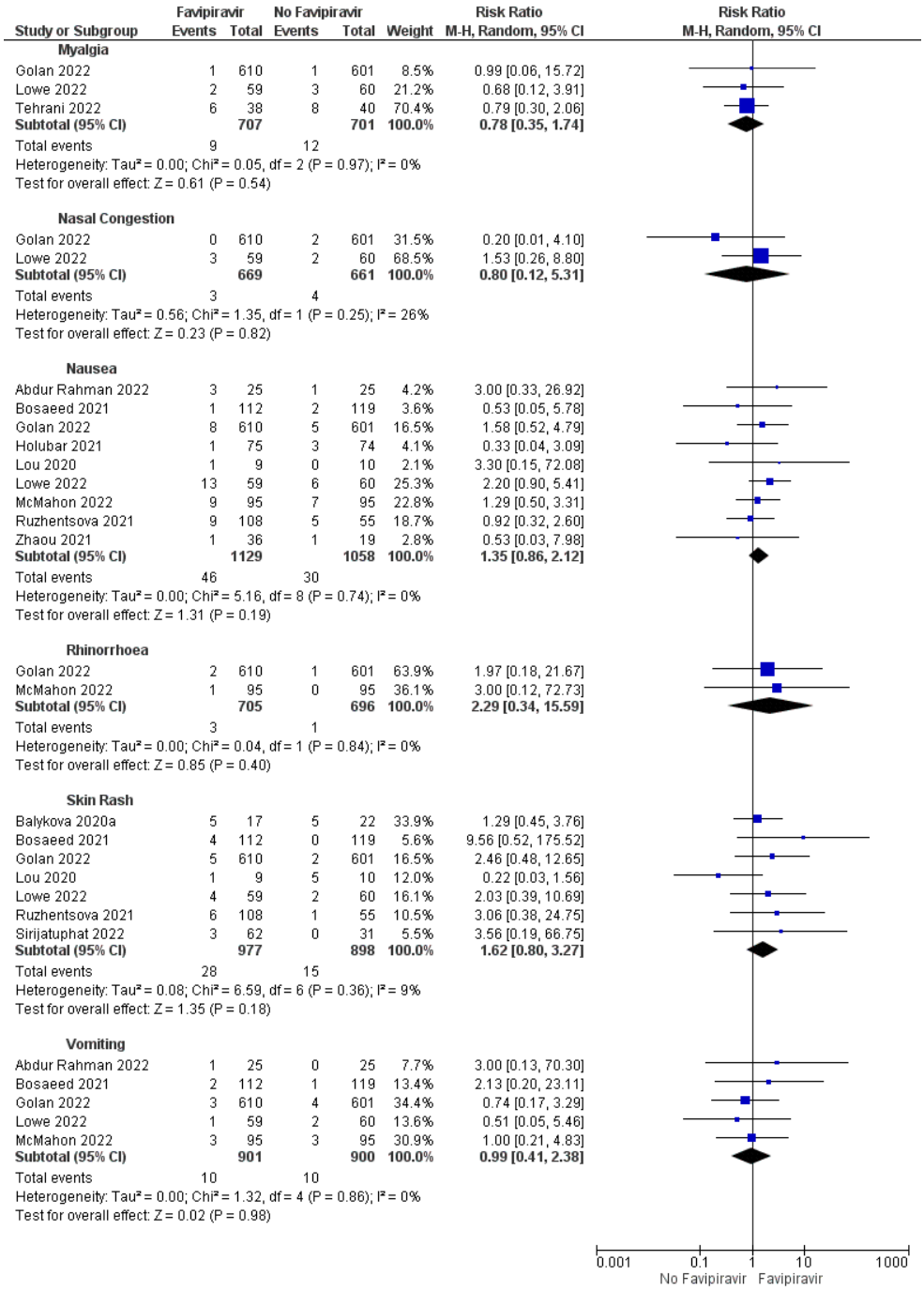
Appendix 3.9 Forest plots for safety outcomes: blood related parameters



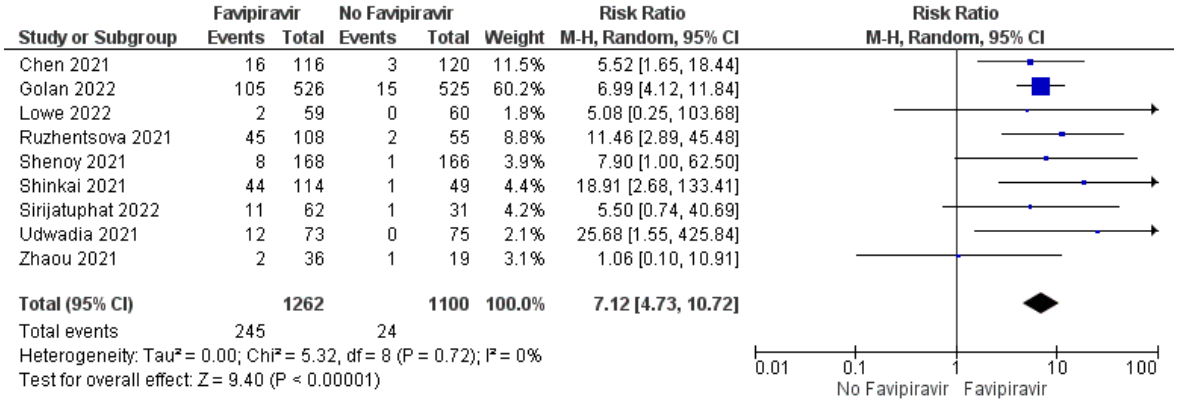
Appendix 3.10 Forest plots for safety outcomes: abdominal pain, anorexia, constipation, diarrhea, dizziness, dyspnea, headache, myalgia, nasal congestion, nausea, rhinorrhoea, skin rash, and vomiting



Appendix 3.10 Forest plots for safety outcomes: abdominal pain, anorexia, constipation, diarrhea, dizziness, dyspnea, headache, myalgia, nasal congestion, nausea, rhinorrhoea, skin rash, and vomiting

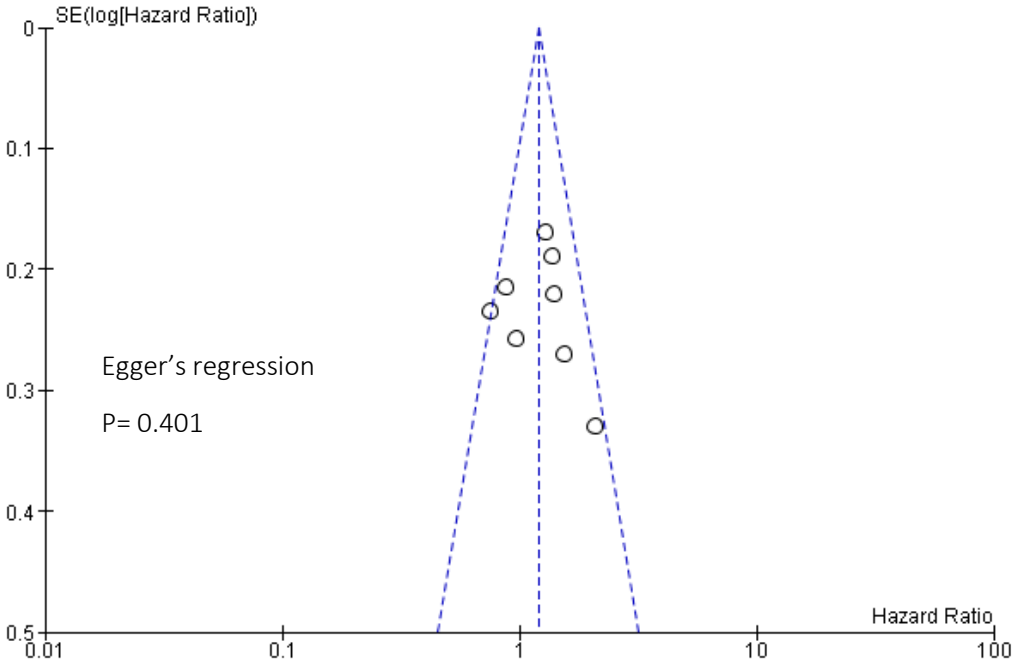


Appendix 3.11 Forest plots for sensitivity analysis of hyperuricemia results

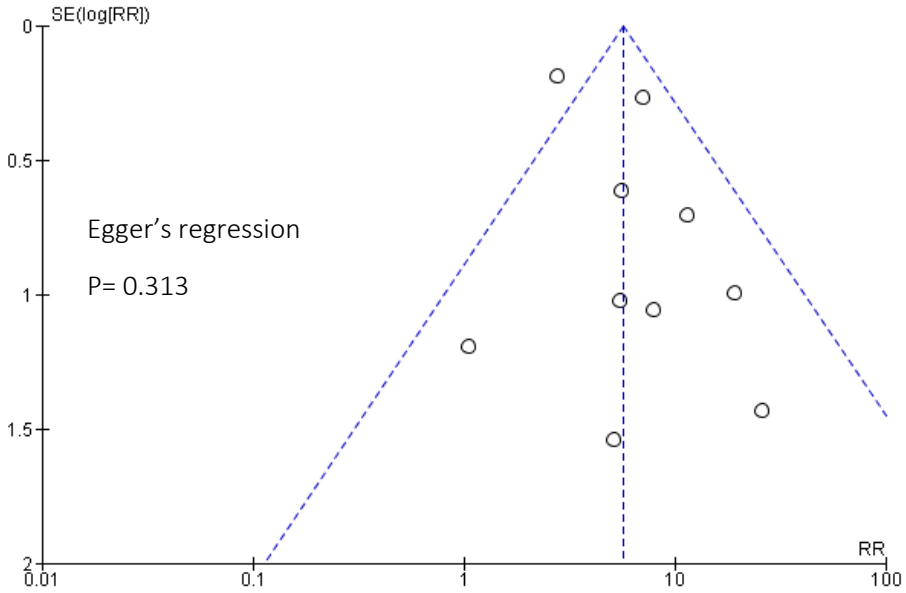


Appendix 3.12 Funnel plots for viral clearance and hyperuricemia

a. viral clearance



b. hyperuricemia



Appendix-Study IV: Pharmacist's Knowledge, Perception, and Readiness Toward Telepharmacy

Appendix 4.1 Sociodemographic Characteristics of Participants

Name	:			
Pharmacist ID No.	:			
Email	:			
Age in years	:	□ 17-25	□ 36-45	□ 56-65
		□ 26-35	□ 46-55	□ ≥ 65
Gender	:	□ Male	□ Female	
Education	:	□ Pharmacist	□ Master/ Doctoral	
Field of Work	:	□ Community Pharmacy		
		□ Hospital		
		□ Public Health Center		
Internet Access	:	□ Stable	□ Unstable/ Poor	
Residence	:	□ Rural	□ Urban	
Province	:	**West Region**	**Central Region**	**East Region**
		□ Aceh	□ Bali	□ Maluku
		□ North Sumatera	□ West Nusa Tenggara	□ North Maluku
		□ West Sumatera	□ East Nusa Tenggara	□ West Papua
		□ Riau	□ South Kalimantan	□ Papua
		□ Jambi	□ East Kalimantan	
		□ South Sumatera	□ North Kalimantan	
		□ Bengkulu	□ North Sulawesi	
		□ Lampung	□ Central Sulawesi	
		□ Bangka Belitung	□ South Sulawesi	
		□ Riau Islands	□ Southeast Sulawesi	
		□ Jakarta	□ Gorontalo	
		□ West Java	□ West Sulawesi	
		□ Central Java		
		□ Yogyakarta		
		□ East Java		
		□ Banten		
		□ West Kalimantan		
		□ Central Kalimantan		

Appendix 4.2 Knowledge (K), Perception (P), Readiness (R) Items Toward Telepharmacy

Item Code	Questions	Answer	
		Yes	No
K1	Telepharmacy is the provision of pharmaceutical care at a distance through information and communication technology by pharmacists.		
K2	Telepharmacy services can be conducted using electronic technology tools such as video conferencing, new systemic software applications, and an automatic dispensing machine.		
K3	Telepharmacy requires a strong internet connection or high-performance technology.		
K4	Telepharmacy provides better counseling in terms of privacy and the length of the session.		
K5	Counseling via telepharmacy is more expensive.		
K6	Pharmacists play an important role in telepharmacy services for patient health care.		
K7	Telepharmacy can assess pharmacists' perceptions of pharmaceutical care.		
K8	Telepharmacy is also involved in ADR monitoring and reporting		

Item Code	Questions	Answer				
		SD	D	N	A	SA
P1	Do you think telepharmacy will improve the patient's adherence to the medication?					
P2	Do you feel telepharmacy will enhance the patient's access to medication?					
P3	Do you think telepharmacy is able to help patients save money and travel time to reach healthcare facilities?					
P4	Do you think therapy monitoring by telepharmacy would be cost-effective compared to a direct consultation at a pharmacy?					
P5	Do you pharmacy schools should provide education programs encompassing topics on computational skills, information technology, and telepharmacy to assist in the future utilization of telepharmacy?					
P6	Do you think patient consultation via telepharmacy will be effective?					
P7	Do you think telepharmacy will provide a complete privacy setting during the consultation period?					
P8	Do you think telepharmacy helps improve communication among healthcare providers?					

Note: SD, Strongly Disagree; D, Disagree; N, Neutral; A, Agree; SA, Strongly Agree

Item Code	Questions	Answer				
		SD	D	N	A	SA
R1	I am ready to work on telepharmacy projects even in rural areas without an incentive.					
R2	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.					
R3	I am ready to teach the patients how to use their drug delivery device (e.g., inhaler, insulin pen) properly through video consultation.					
R4	I am willing to undergo training in ethics and legal issues related to telepharmacy.					
R5	I am ready to face the implementation of telepharmacy in all healthcare settings.					
R6	I am ready to improve and reduce the risk of medication errors among patients through telepharmacy.					
R7	I am ready to conduct medication reconciliation via telepharmacy services.					
R8	I am ready to carry the increased workload when conducting telepharmacy.					

Note: SD, Strongly Disagree; D, Disagree; N, Neutral; A, Agree; SA, Strongly Agree

Appendix 4.3. Item-Level Statistics: Internal Consistency, Convergent Validity, and Discriminant Validity Scores

Item Code	Questions	Loading Factor	AVE	α	ρc
Knowledge			0.788	0.961	0.967
K1	Telepharmacy is the provision of pharmaceutical care at a distance through information and communication technology by pharmacists.	0.939			
K2	Telepharmacy services can be conducted using electronic technology tools such as video conferencing, new systemic software applications, and an automatic dispensing machine.	0.845			
K3	Telepharmacy requires a strong internet connection or high-performance technology.	0.911			
K4	Telepharmacy provides better counseling in terms of privacy and the length of the session.	0.945			
K5	Counseling via telepharmacy is more expensive.	0.858			
K6	Pharmacists play an important role in telepharmacy services for patient health care.	0.955			
K7	Telepharmacy can assess pharmacists' perceptions of pharmaceutical care.	0.706			
K8	Telepharmacy is also involved in ADR monitoring and reporting.	0.914			
Perception			0.779	0.959	0.966
P1	Do you think telepharmacy will improve the patient's adherence to the medication?	0.883			
P2	Do you feel telepharmacy will enhance the patient's access to medication?	0.912			
P3	Do you think telepharmacy is able to help patients save money and travel time to reach healthcare facilities?	0.892			
P4	Do you think therapy monitoring by telepharmacy would be cost-effective compared to a direct consultation at a pharmacy?	0.808			
P5	Do you think pharmacy schools should provide education programs encompassing topics on computational skills, information technology, and telepharmacy to assist in the future utilization of telepharmacy?	0.878			
P6	Do you think patient consultation via telepharmacy will be effective?	0.878			
P7	Do you think telepharmacy will provide a complete privacy setting during the consultation period?	0.883			
P8	Do you think telepharmacy helps improve communication among healthcare providers?	0.920			
Readiness			0.795	0.963	0.969
R1	I am ready to work on telepharmacy projects even in rural areas without an incentive.	0.780			
R2	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.	0.912			
R3	I am ready to teach the patients how to use their drug delivery device (e.g., inhaler, insulin pen) properly through video consultation.	0.920			
R4	I am willing to undergo training in ethics and legal issues related to telepharmacy.	0.922			
R5	I am ready to face the implementation of telepharmacy in all healthcare settings.	0.932			
R6	I am ready to improve and reduce the risk of medication errors among patients through telepharmacy.	0.928			
R7	I am ready to conduct medication reconciliation via telepharmacy services.	0.908			
R8	I am ready to carry the increased workload when conducting telepharmacy.	0.817			

AVE, average variance extracted, α, Cronbach's alpha; ρc, composite reliabilities;