Sys Rev Pharm 2021; 12(4): 6-13
A multifaceted review journal in the field of pharmacy
E-ISSN 0976-2779 P-ISSN 0975-8453

Research Article

Systematic Review: Economic Evaluation of Treatment for Human Epithelial Growth Factor Receptor 2-positive Metastatic Breast Cancer from a National Health Insurance Perspective

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Article History: *Submitted: 26.03.2021* *Accepted: 09.04.2021* *Published: 13.04.2021*

ABSTRACT

Background: Economic evaluation is often held from the societal perspective. Even it is important, as the therapy affects greatly to the patients' life in society, economic evaluation from the payer perspective, is as important as it may help National Health Insurance (NHI) as the payer avert budget deficit as was observed in Indonesia. Unfortunately economic evaluation from the payer's perspective is very rare to be done. This article compiles and reviews research articles of economic evaluation of therapy for human epithelial growth factor receptor 2-positive metastatic Breast Cancer (mBC) as an alternative to trastuzumab therapy, which has recently been removed from Indonesia's National Health Insurance coverage.

Methods: The literature search was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations and PICO methodology (Population, Intervention, Comparison, and Outcome). Relevant articles were retrieved from online biomedical databases Scopus, PubMed, ScienceDirect, and SAGE Journals. Quality appraisal was performed using a standardized checklist which consisted of items in the CHEC checklist.

Results: A total of six articles pertaining to economic evaluation of therapy for HER2-positive mBC from the NHI perspective (period: 2008–2018) were reviewed. Trastuzumab+chemotherapy showed the longest overall survival (OS, 37.8 months) with Progression-free Survival (PFS) of 12.7 months. Trastuzumab+docetaxel as 1st line therapy were associated with the longest PFS (19 months) with a total cost of US$ 12,732. With respect to therapy sequence, 1st line, trastuzumab+pertuzumab+docetaxel; 2nd line, trastuzumab+emtansine ; and 3rd line, lapatinib+capecitabine was associated with the highest quality-adjusted life year (QALY; 1.81) but also the highest total cost and incremental cost (US$360,880 and US$197,250, respectively). The sequence of 1st line, trastuzumab/docetaxel; 2nd line, T-DM1; and 3rd line, trastuzumab/lapatinib was associated the lowest QALY (1.27) but was the most cost-effective (total cost: $158,293). Lapatinib+capecitabine as 2nd line therapy and exemestane monotherapy were associated with the lowest total cost (US$3,190).

Conclusion: Lapatinib+capecitabine as 2nd line therapy and exemestane monotherapy show potential as alternatives to trastuzumab therapy for HER-2 positive mBC.

Keywords: Economic evaluation; mBC; HER2 positive; NHI.

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INTRODUCTION

Cancer is one of the most common causes of death worldwide. According to the Asean Costs in Oncology, mortality rates of cancer patients approach 70% despite the high economic burden imposed by treatment costs [1]. The prohibitive costs of cancer therapy and the need for long-term treatment pose a grave financial threat to the patients and their families [2]. In this context, implementation of National Health Insurance (NHI) with coverage for anticancer therapy is highly recommended [3].

Globally, breast cancer is the most frequent cancer that affects more than 1.5 million women every year; it is also the greatest contributor to cancer-related deaths, (estimated deaths from breast cancer in 2015: 570,000) [4]. About 5%-10% of BC cases are estimated to be metastatic at diagnostic, whereas 20%-30% of early BC cases will eventually become metastatic despite the therapy development [5-7].

Human epithelial growth factor receptor 2 (HER2)-positive breast cancer accounts for 20–25% of the total cases of breast cancer [8]. Indonesian NHI health-financing through BPJS Kesehatan covers trastuzumab therapy for HER2-positive (+++) metastatic breast cancer (mBC) [9]. The decree allows coverage for 8 cycles of trastuzumab therapy for each patient, while lapatinib is recommended as the second line therapy for HER2-positive (+++) mBC.

The US Food and Drug Administration have already approved the use of trastuzumab, pertuzumab, and lapatinib for treatment of mBC [10]. Trastuzumab was shown to improve the survival rates and quality of life of patients with mBC with a minimum of 18 cycles in a year (once every three weeks) [11]; however, the treatment costs are often regarded too high for the NHI. From 1 April 2018, Indonesia's NHI has stopped the coverage for trastuzumab. Although the decision is quite controversial, the high price and the lack of consensus on the indications for mBC therapy were the main reasons for the de-

cision [12]. The budget deficit in Indonesia's NHI also contributed to the decision-making.

Miscalculated decision for coverage of therapy options will potentially lead to budget deficit for the payers. A systematic review of economic evaluation of treatment for HER2-positive mBC from the perspective of NHI is largely lacking. In this study, we aimed to provide an overview of evidence from economic evaluation of treatment for HER-2 positive mBC from across the world as a preliminary study for economic evaluation of Indonesia's NHI coverage of HER2-positive mBC as an alternative to the recently cancelled trastuzumab therapy. In this study, we performed a systematic review of studies pertaining to the economic evaluation of the National Health Insurance coverage for cancer treatment across the world.

METHODS

Search strategy

The literature search was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations followed by PICO methodology (population, intervention, comparison, and outcome), using NHI participants as the observed population; HER2 positive mBC therapy as the intervention; HER2 positive mBC therapy variation as the comparison; and the result of economic evaluation as the outcome [13]. We conducted a systematic search of relevant literature on Scopus, PubMed, ScienceDirect, and SAGE Journals using the following key words: "economic evaluation" OR "cost-effectiveness analysis" AND "HER2 positive metastatic breast cancer", while considered the inclusion criteria and exclusion criteria. The inclusion criteria were economic evaluation, specific for HER2-positive mBC, from NHI perspective, full-text research articles, published in English language, and published between 2008 and 2018. Other articles that not related to the inclusion criteria were excluded [14,15].

Data synthesis

General information on authors, country of study, year of publication, perspective, study population, and comparators were obtained from the retrieved articles. Through a systematic selection process, the decision analytic model characteristics, study period, study outcomes, discounts, and results were also retrieved. When the information was not clearly stated in the articles, it was labeled as "unclear/not stated" to avoid misinterpretation. The following study outcomes were extracted: quality-adjusted life year (QALY), total costs for each comparator, incremental QALY (iQALY), and incremental cost-effectiveness ratio (ICER). Total costs, incremental cost, and ICERs were converted to the year 2018 by using the Consumer Price Index of each country and were adjusted to US$ 2018.

RESULTS

A total of 149 articles were retrieved. Eleven articles were excluded because of duplication. After screening of titles and abstracts, 17 were excluded for various reasons [abstracts (7), oral presentation (1), and poster presentation (1)]. From the 104 retrieved full-text articles, 95 were excluded because of various reasons [date of publication prior to 2008 (8); absence of economic evaluation (40); literature reviews (23), non-English language publication (1), not specific for mBC (20), not specific for HER2-positive (7), and not from NHI perspective (7)]. Finally, six journal articles were selected for the literature review [8,16-20]. Table 1 shows the general characteristics of the reviewed studies.

Quality appraisal

Quality appraisal was performed using a standardized checklist which consisted of items in the CHEC checklist and some additional items as described by Soto [14,15]. With some modifications, the checklist consisted of 25 items. The quality indicators were scored as follows: yes/complete details are available in the text (1); no/no details are available or not clearly stated within the text references given (0). The number of items rated as "yes/complete details given" were summed up for each study in order to obtain an indication of study quality. Table 2 shows the results of the quality appraisal of individual studies assessed according to the checklist.

Table 1: General characteristics of the reviewed studies.

No	Authors	Country	Publication Year	Perspective	Type of Economic evaluation	Study Design and Population	Comparison	Decision analytic model	Time horizon	Outcomes	Discount
1.	Benjamin et al.[16]	France	2013	French Health Insurance	BIA	Cohort: All patients with progressive HER2-positivemBC (previously treated with chemotherapy or trastuzumab in the metastatic setting)	Trastuzumab beyond disease progression as 2nd line therapy lapatinib+-capecitabine as 2nd line therapy	Budget impact model	3 years (2012–2014)	Annual treatment cost per patient	N.R.

2.	Diaby et al.[8]	United States	2016	U.S Centers for Medicaid and Medicare Services (CMS)	CEA	Prospective cohort study: Patients	1st Line: Trastuzumab+pertuzumab+Docetaxel (THP) 2nd Line: Trastuzumab+emtansine (T-DM1) 3rd Line: lapatinib+capecitabine 1st line: THP 2nd line: Trastuzumab+lapatinib 3rd line: Trastuzumab+-capecitabine 1st Line: Trastuzumab/docetaxel 2nd Line: T-DM1 3rd Line: Trastuzumab/lapatinib 1st line Trastuzumab+docetaxel without subsequent T- DM1 or pertuzumab 2nd Line: Trastuzumab + lapatinib 3rd Line: Trastuzumab+-capeci-Tabine	Markov model	Lifetime	PFS OS QALYs iQALY NMB ICER Total cost	3.5 % annual rate, converted into a weekly discount Rate
3.	Diaby et al.[20]	United States	2014	US healthcare government-run payer (Medicare)	CEA	Cohort: Population was not reported	Everolimus+exemestane Exemestane	Markov model	120 weeks	QAPFW QAPFY Incremental cost ICER	3.5 % annual rate, converted into a 6-week discount
4.	Leung, Chan, & Wang [17]	Taiwan	2018	Taiwan National Health Service (NHS)	CUA	Cohort: Patients with mBC from January 1, 2009, to December 31, 2011.	Trastuzumab+docetaxel without prior chemotherapy Docetaxel	Markov model	5 years	NMB QALY Incremental cost ICER	3%

5.	Nerich et al. [19]	France	2013	French Public Healthcare System	CMA	Retrospective cohort: Patients with mBC treated by first-line Trastuzumab plus taxane-based chemotherapy	1st line: Trastuzumab+docetaxel 1st line: Trastuzumab+Paclitaxel	N.R.	2001–2010	PFS Total costs	4%
6.	Parkinson et al. [29]	Australia	2016	Australian Government	CEA	Randomized controlled trial (RCT): Patients treated with Trastuzumab between 2001 and 2010	Trastuzumab+chemotherapy Trastuzumab	N.R.	2001–2010	PFS OS	N.R.

BIA: Budget Impact Analysis; CEA: Cost-effectiveness Analysis; CUA: Cost-utility Analysis ;CMA: Cost-minimization Analysis; PFS: Progression-free Survival; OS: Overall Survival; QALYs: Quality Adjusted Life Years; iQALY: incremental QALY; NMB: Net Monetary Benefit; ICER: Incremental Cost-effectiveness Ratio; QAPFW: Quality-adjusted Progression-free Survival Weeks; QAPFY: Quality-Adjusted Progression-free Years; mBC: metastatic Breast Cancer; N.R.: Not Reported

Table 2: Quality appraisal of economic evaluation of HER2-positive metastatic breast cancer therapy from a national health insurance perspective.

No	Questions	Study					
	Research question	16	8	20	17	19	29
1	Does a well-defined objective exist? Is it clear and answerable?	1	1	1	1	1	1
2	Are the alternatives described?	1	1	1	1	1	1
3	Is the payers perspective used?	1	1	1	1	1	1
4	Is it justified why the perspective is used?	1	0	1	1	1	1
5	Is a lifetime horizon taken into account?	0	1	0	1	0	0
6	Are reasons for another time horizon incorporated?	1	0	1	0	0	0
Model description							
7	Is the type of model used in the study stated clearly?	1	1	1	1	0	0
8	Are details of the model given?	1	1	1	1	0	0
9	Is the design of the model appropriate and does it include the correct health states?	1	1	1	1	0	0
Model data sources							
10	Are the sources of all values credible and accurate?	1	1	1	1	0	0
11	Are assumptions incorporated into the model clearly stated?	1	1	1	1	0	0
Outcomes							
12	Are all important and relevant outcomes for each alternative identified?	1	1	1	1	1	1
13	Are the probabilities that outcomes happen clearly stated?	1	1	1	1	0	0
14	Are all outcomes measured appropriately?	1	1	1	1	1	1
15	Are outcomes valued appropriately?	1	1	1	1	1	1
Costs							
16	Are all important and relevant costs for each alternative identified	1	1	1	1	1	1
17	Are all costs measured appropriately in physical units?	1	1	1	1	1	1
18	Are costs valued appropriately?	1	1	1	1	1	1
19	Are all future costs and outcomes discounted appropriately?	0	1	1	1	1	0

Incremental and sensitivity analysis							
20	Is an incremental analysis of cost and outcomes of alternatives performed?	0	1	1	1	0	0
21	Is a one-way sensitivity analysis performed?	1	0	1	1	1	0
22	Is a probabilistic sensitivity analysis performed?	1	1	1	1	0	0
Discussion and conclusion							
23	Do the conclusions follow from the data reported?	1	1	1	1	1	1
24	Does the study discuss the generalizability of the results to other settings and patient/client groups?	0	0	0	0	0	0
25	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	1	1	1	1	1	1
26	Are ethical and distributional issues discussed appropriately?	1	0	0	0	0	1
	Total	22	21	23	23	14	13
Yes/complete details are given in text (1); no/no details are available or not clearly stated within the text references given (0)							

A total of seven categories were appraised in the retrieved articles. This included research question, model description, data sources for the used model, outcomes and probabilities, costs, incremental and sensitivity analysis. The research objectives and research process were clearly defined for all six studies along with the description of alternative comparators. The hospital perspective was used in all studies. One study failed to justify the use of the payer perspective. Only two studies took into account the lifetime horizon and only two studies justified the incorporation of another time horizon.

In two studies, health states of the model were neither mentioned nor graphically represented. This hampered the assessment of the appropriateness of the model for the decision problem. The lack of description of models and calculations is known to hinder the analysis and the reliability of the published articles [18]. The authors were unable to assess the credibility and accuracy of the sources of all values because of the lack of clear reporting.

Sensitivity analysis is used to test the robustness of results [21-23]. Four studies performed one-way sensitivity analysis. Four studies also performed deterministic and probabilistic sensitivity analyses to assess the uncertainty of the model and to evaluate the overall robustness.

Related to the obtained outcomes, five of these studies had reported relevant outcomes for each of the compared alternatives. Rather than focusing on the non-clinical outcomes, one study focused on patient survival throughout the given therapies. In the three studies, the incremental analysis was not performed. Ethical and distributional issues were observed in two studies. None of the studies discussed the generalizability of the results. The studies fulfilled on average 20 out of the 26 items on the checklist (range, 13–23).

Cost according to a payer perspective is a cost incurred by an insurer or NHI, in the form of a hospital claim for health services [24]. Components that are frequently assessed include effectiveness, cost-effectiveness, safety, and quality of life. Outcomes measured in the economic evaluation include clinical and non-clinical outcomes. A typical example of clinical outcome is the number of years of survival, while QALY or disability-adjusted life years are commonly used as the non-clinical outcomes.

All the six articles suggest different therapy options for HER2-positive mBC. From the reviewed articles, both clinical and non-clinical outcomes were obtained. The obtained non-clinical outcomes were then converted to the year 2018 value by using the Consumer Price Index (CPI) of each country and adjusted to US$ 2018 CPI using CPI inflation calculator from the Bureau Labor of Statistics. A summary of the outcomes of the reviewed studies is presented in Table 3.

DISCUSSION

Economic evaluation is a part of multidisciplinary Health Technology Assessment (HTA) that helps policymakers decide which health technologies, including medicinal therapies to include in the NHI coverage [25]. It essentially aims to prioritize the use of scarce fund resources to meet unlimited human needs. The economic evaluation assesses the worth of a particular procedure, service, or program in comparison to that of an alternative in resource-constrained settings [24,26]. In the health sector, there are two types of economic evaluation: partial and full economic evaluation [27].

There are three types of partial economic evaluation: economic evaluation that assesses only one outcome or cost description without comparison to other alternatives; a cost-outcome description with no comparison to other alternatives; and economic evaluation that covers only the evaluation of the effectiveness or cost analysis without comparison to other alternatives. Full economic evaluation considers both costs and outcomes in comparison to other alternatives. It includes: Cost-minimization Analysis (CMA); Cost-effectiveness Analysis (CEA); Cost-utility Analysis (CUA); and cost-benefit analysis.

HTA also requires Budget Impact Analysis (BIA) after the implementation of economic evaluation. BIA should be performed even if the health technology is not found to be cost-effective because it is needed by the community. The description of the implications for the budget or BIA is used to help the payers estimate the implications of the amount of money needed for new interventions/health technologies that have been proposed to the decision-makers, compared to the cost of the current intervention[24].

Over the years, CEA has been extensively used to support reimbursement decision for treatment of mBC [28]. The scarcity of CEA studies for HER2-positive mBC is attributable to the relative lack of economic evaluation from the payer perspective, as economic evaluation from the societal perspective is considerably more recommended [24]. We believe that economic evaluation from the payer perspective is as important as it may help avert budget deficit as was observed in Indonesia. Therefore, meticulous calculations to inform therapy coverage decision-making, especially for high-cost therapies such as mBC therapy, is a key imperative. The cancellation of coverage for trastuzumab by Indonesia's NHI is the cause of conflict and disconcertion among the patients and healthcare providers as it is deemed to be the most appropriate option for HER2-positive mBC. Lack of awareness-raising about the cancellation of the coverage among the public and healthcare providers also contributed to the strong denial. A study of the more

Table 3: Summary of outcomes of the reviewed studies.

Authors	Economic evaluation	Comparison	Outcomes								
			Clinical						Non- clinical (US$)		
			OS	TTP	PFS	QALY	iQALY	QAPFW	ICER	Total cost	Incremental cost
Benjamin et al. [16]	BIA	2ndline: Trastuzumab	N.R.	8.6 months	N.R.	N.R.	N.R.	N.R.	N.R.	6,703	N.R.
		2ndline: lapatinib+capecitabine	N.R.	N.R.	4.2 months	N.R.	N.R.	N.R.	N.R.	3,190	N.R.
Diaby et al. [8]	CEA	1st Line: Trastuzumab+pertuzumab+docetaxel (THP) 2nd Line: Trastuzumab+emtansine (T-DM1) 3rd Line: lapatinib+capecitabine	N.R.	N.R.	N.R.	1.81	N.R.	N.R.	N.R.	360,880	197,250
		1st line: THP 2nd line: Trastuzumab+lapatinib 3rd line: Trastuzumab+-capecitabine	N.R.	N.R.	N.R.	1.78	N.R.	N.R.	N.R.	359,336	18,4547.01
		1st Line: Trastuzumab/docetaxel 2nd Line: T-DM1 3rd Line: Trastuzumab/lapatinib	N.R.	N.R.	N.R.	1.27	N.R.	N.R.	N.R.	158,293	-
		1st line: Trastuzumab+docetaxel without subsequent T-DM1 or pertuzumab 2nd Line: Trastuzumab + lapatinib 3rd Line: Trastuzumab+-capeci-Tabine	N.R.	N.R.	N.R.	1.41	N.R.	N.R.	N.R.	185,858	27,565
Leung, Chan, & Wang [17]	CEA	Trastuzumab+docetaxel without prior other chemotherapy	18.5 months	N.R.	N.R.	N.R.	0.09 QALY	N.R.	164,420	164,420	14,119
		Docetaxel	17.5 months	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.
Parkinson et al. [29]	CEA	Trastuzumab+chemotherapy	37.8 months	N.R.	12.7 months	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.
		Trastuzumab	23.6 months	N.R.	4.0 months	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.
Diaby et al. [20]	CEA	Everolimus+exemestane	N.R.	N.R.	N.R.	N.R.	N.R.	5.31 months	N.R.	67,376	64,186
		Exemestane	N.R.	N.R.	N.R.	N.R.	N.R.	2.34 months	N.R.	3,190	-
Nerich et al.[19]	CMA	1st line: Trastuzumab+docetaxel	N.R.	N.R.	19 months	N.R.	N.R.	N.R.	N.R.	12,732	N.R.
		1st line: Trastuzumab+Paclitaxel	N.R.	N.R.	17 months	N.R.	N.R.	N.R.	N.R.	12,317	N.R.

BIA: Budget Impact Analysis; CEA: Cost-effectiveness Analysis; CUA: Cost-utility Analysis ;CMA: Cost-minimization Analysis; PFS: Progression-free Survival; OS: Overall Survival; QALYs: Quality Adjusted Life Years; iQALY: incremental QALY; NMB: Net Monetary Benefit; ICER: Incremental Cost-effectiveness Ratio; QAPFW: Quality-adjusted Progression-free Survival Weeks; QAPFY: Quality-Adjusted Progression-free Years; mBC: metastatic Breast Cancer; N.R.: Not Reported

economical alternative therapy which has similar potential efficacy as trastuzumab is needed to alleviate the tension in public.

The six studies reviewed evaluated treatment of HER2-positive mBC from a NIH perspective. One study performed BIA which is the final step of economic evaluation. BIA is generally used by the decision makers to explain the probability of treatment and cost alteration from particular diseases. All of the remaining studies involved full economic evaluation. Three of these studies performed CEA, one study performed CUA, and one study performed CMA.

Due to limited comparability of the variables, direct comparison of the data is limited. With respect to survival outcomes, trastuzumab+chemotherapy showed best OS (37.8 months) and PFS (12.7 months); however, the economic value is not clear as the authors had focused on the clinical outcomes [29]. Considering the obtained PFS, trastuzumab+docetaxel as the 1st line therapy resulted in the longest PFS of 19 months but was associated with the highest total cost of treatment (US$ 12,732) [19].

The therapy sequence of 1st line, trastuzumab+pertuzumab+docetaxel (THP); 2nd line, trastuzumab+emtansine (T-DM1); and 3rd line, lapatinib+capecitabine; was the most clinically effective (QALY 1.81); however, its cost implications were also the highest (total cost: US$360,880; incremental cost: US$197,250) [8]. The least clinically effective therapy sequence (QALY 1.27) yet most cost-effective was 1st line, trastuzumab/Docetaxel; 2nd line, T-DM1; and 3rd line, trastuzumab/lapatinib (total cost: $158,293) [8].

Lapatinib+capecitabine as the 2nd line therapy and exemestane monotherapy were associated with the lowest total cost (US$3,190) [16]. A study by Benjamin et al. found that the higher cost of the oral drug is offset by cost savings accruing from the averted need for intravenous chemotherapy and medical transportation costs [16]. The cost of medical investigations to monitor cardiotoxicity and physician consultation costs during follow-up also contribute to the higher costs. Decreasing the overall healthcare cost of treatment of HER2-positive mBC is important to relieve excessive expenditure on cancer therapy.

From the available studies, trastuzumab still dominates as the therapeutic option for HER2-positive mBC. Apart from the trastuzumab existence in the therapy sequence, lapatinib+capecitabine as 2nd line therapy and exemestane monotherapy show potential as alternative for HER-2 positive mBC.

LIMITATIONS

The limitations of this review include the potential studies missed during the literature search process. The authors were re-did the articles selection process for multiple times both in group and individually, and then discuss the result to minimize the potential risk and bias. The relative lack of data pertaining to the same type of economic evaluation was another constraining factor in this review.

CONCLUSION

There are numerous outcomes in economic evaluation. The heterogeneity among the included studies with respect to the variables and outcomes and the lack of comparability between the alternative therapies was a major constraint in this review. Hence, the clinical and non-clinical outcomes could not be compared directly. From the reviewed studies, lapatinib+capecitabine as 2nd line therapy and exemestane monotherapy show potential as alternatives to trastuzumab therapy that can be used for NHI coverage therapy option for patients with HER-2 positive mBC in Indonesia.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Bambang Wispriyono, Ph.D. for his advice and support. This study was supported by grants from the Universitas Indonesia through Hibah Publikasi Internasional Terindeks untuk Tugas Akhir Mahasiswa (Hibah PITTA) 2018 or Indexed International Publication for Student's Final Project funding No. 2186/ UN2.R3.1/HKP.05.00/2018.

COMPLIANCE WITH ETHICAL STANDARDS

Competing interest

The authors certify that they have no conflict of interest with any individuals or organizations related to the manuscript materials.

Ethics approval and consent to participate

This study has been approved by the Ethics Committee and Community Service of Faculty of Public Health, Universitas Indonesia No. 675/ UN2.F10/PPM.00.02/2018.

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