

# Prediction of Relative Risk "SUSPECT" and "CONFIRM" COVID-19 Using Meta-Analysis Approach

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## ABSTRACT

**Background:** Coronavirus Disease 2019 (COVID-19) is a disease caused by a new type of virus called Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). The number of COVID-19 cases in Indonesia continues to increase every day, followed by an increasing number of deaths. During a pandemic like this, it is important for a country to control the rate of increase in Covid-19 patients and the rate of patient mortality from Covid-19 disease. As a real first step in determining who is affected by Covid-19 and not, this is what is important, and then there will be appropriate handling of each of the positive and negative ones. If the treatment is right, then the handling will be good and have an impact on a lower risk of death.

**Materials and Methods:** This study uses secondary data per district of Sidoarjo Regency, which is obtained from <https://covid19.sidoarjo.jab.go.id/#angka> as of 13/12/2020 at 17.00 WIB. The data obtained are data on the number of "Suspect" and "Confirm" COVID-19, for each district in Sidoarjo Regency. The method of analysis in this research is meta-analysis for binary data ("Suspect" or "Confirm") which will calculate the effect size in the form of a risk ratio, risk difference, and odds ratio. Furthermore, to determine the prediction of pessimistic, actual and optimistic risks for the "Suspect" and "Confirm" groups who experienced the event (died).

**Results:** Relative risk groups can be grouped into 3 parts. Group 1 consists of a relative risk of less than 0.225, namely Sidoarjo district (0.051), Jabon district (0.036), Krembung district (0.069), Tulangan district (0.123), and Krian district (0.028). Group 2 consists of relative risks from 0.225 to 0.567, namely Buduran district (0.258), Candi district (0.414), Porong district (0.470), Taman district (0.317), Sedati district (0.274), Waru district (0.252), and Tarik district (0.301). Group 3 consists of risks above 0.567, namely Gedangan district (0.645), Tanggulangin district (1.353), Wonoayu district (0.748), Prambon district (0.790), Sukodono district (1.070), and Balongbendo district (0.728). The results of the forest plot in Relative Risk (log scale) Group 1, hereinafter referred to as the green zone, are in Sidoarjo district, Buduran district, Jabon district, Taman district, Krembung district, Tulangan district, Krian district, Sedati district, Waru district, and Tarik district. Group 2, hereinafter referred to as the Yellow Zone, is in the Candi subdistrict, the Gedangan subdistrict, the Porong subdistrict, the Wonoayu district, the Prambon subdistrict, and the Balongbendo district. Group 3, hereinafter referred to as the Orange Zone, is in the Tanggulangin district and Sukodono district.

**Conclusion:** The "Confirm" group had a greater risk of dying than the "Suspect" group. The districts in Sidoarjo Regency with the highest risk of dying in confirmed cases are Tanggulangin district, Wonoayu district, Prambon district, Sukodono district. While the lowest relative risk of dying was in Krian district, Jabon district, Krembung district and Sidoarjo district.

**Keywords:** "Suspect", "Confirm", COVID-19, random effect, relative risk, forest plot

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## INTRODUCTION

The outbreak of the Corona virus infection that emerged in Wuhan, China, has not yet ended. In Indonesia itself, positive cases of COVID-19 have continued to increase every day since it was first confirmed in March 2020. COVID-19 is a new disease caused by the novel coronavirus, which is a new virus that comes from the same family as Severe Acute Respiratory Syndrome (SARS) and some types of the common cold. This disease was first identified in Wuhan, China in 2019 and to date has spread to various countries around the world very quickly [1]. WHO has declared that COVID-19 is a public health emergency of international concern. As of February 25, 2020, a total of 81,109 laboratory confirmed cases have been documented globally [2] [3]. Therefore, the government continues to make various efforts to overcome this disease outbreak in Indonesia. One of them is by holding surveillance or monitoring activities that are

tighter and making various efforts to prevent Corona virus infection at every level of society.

Covid-19 (Coronavirus disease) is an infectious disease caused by a newly discovered type of coronavirus. This is a new virus and a previously unknown disease prior to the outbreak in Wuhan, China, in December 2019. Coronavirus is a group of viruses that can cause disease in animals or humans. Several types of coronavirus are known to cause respiratory tract infections in humans ranging from cold coughs to more serious ones such as Severe Acute Respiratory Syndrome (SARS). People can catch Covid-19 from other people who have the virus. Covid-19 can be spread from person to person through droplets from the nose or mouth that come out when a person with Covid-19 coughs or exhales. These droplets then fall onto nearby surface objects. People who touch these objects or surfaces and then touch their eyes, nose or mouth, can get Covid-19. Covid-19 transmission can

also occur if people breathe in droplets that come out of the cough or breath of people who have Covid-19 [4]. Until now, the Indonesian government is still trying to carry out massive laboratory examinations to find cases of Covid-19 in the community. This step was taken to track and break the chain of the spread of the corona virus in the country [5]. The first step taken for initial screening is a rapid test. For tests that really determine whether a person has Covid-19 or not, there are at least two tests, namely polymerase chain reaction (PCR) and SWAB antigen. These two tests take samples from the nasopharyngeal cavity and / or oropharynx with the final result being positive for Covid-19 or negative for Covid-19 [6]. The more accurate a test is, the better it will be for health workers to determine what kind of treatment is suitable for patients whose status has been determined for Covid-19 disease.

Handling of COVID-19 cases in Indonesia itself is divided into three status levels, namely People Under Monitoring (ODP), Patients Under Monitoring (PDP) and “Confirm”. ODP usually has mild symptoms such as cough, sore throat, fever, but there is no close contact with positive sufferers. Meanwhile, PDP is criticized according to the symptoms, such as fever, cough, shortness of breath, sore throat or from the observation that the lower respiratory tract is disturbed and there is close contact with positive sufferers or those who are infected. Meanwhile, “Confirm” is a term for a person infected with COVID-19 with a positive laboratory result [7]. Regarding surveillance activities, the Ministry of Health of the Republic of Indonesia through the Decree of the Minister of Health Number HK.01.07 / Menkes / 413/2020 replaced the old operational terms in handling COVID-19 with several new terms, namely Suspect, Probable, Confirmation, and Various New Terms on COVID-19 [8].

Several studies related to the meta-analysis, [9], the results showed that of the 20 studies in the meta-analysis of synthesized binary data there was a relationship between ventilation and the incidence of pulmonary tuberculosis with a significant value of  $p = 0.000 < (\alpha = 0.05)$ , but partially 13 studies are significant and 7 are not significant. Research [10], the results of the T-test model with the implementation of MASEM GLS in MatlabR2018 (GLS-M) show that poverty is influenced by health and human resources with coefficients of -0.2761 and -0.2111

but not influenced by Economics. The accuracy of the poverty model is influenced by exogenous variables of economy, health, and human resources, is 50.6% with a chi-square value of 637.0749. Research [11], a systematic review and meta-analysis of the relationship between COVID-19 and liver injury, shows that COVID-19-related liver injury is more common with severe COVID-19 than non-severe COVID-19. Clinicians should be aware of the possibility of developing severe disease in subjects with COVID19-related liver injury. Meanwhile, research [12], using a systematic reviewer approach and meta-analysis, showed that the most common liver dysfunction is hypoalbuminemia followed by gamma-glutamyl transferase and aminotransferase disorders, and this disorder is more common in severe disease.

The number of COVID-19 cases in Indonesia continues to increase every day, followed by an increasing number of deaths. The cases of COVID-19 that occurred in East Java as of April 9, 2020 were 6.78% of the total cases in Indonesia, where 22.62% of patients were declared cured and 6.07% of patients were declared dead and the rest were under treatment [4]. There were 2,859 cases of positive confirmation of Covid-19 in Sidoarjo Regency. Of the total cases, 1,148 people (40.15 percent) were treated, 1,544 people (54 percent) confirmed cured and 167 people (5.84 percent) died. Meanwhile in the last two weeks there has been a shift in the Covid-19 case in Sidoarjo, from positive over recovery to confirmation of recovery more than positive. although the pattern has not been stable [13]. Therefore, this study will examine the effect size which is a measure to determine the risk prediction of pessimism, actual and optimism for the "Suspect" and "Confirm" groups who experience events (died) in Sidoarjo Regency with the Meta Analysis approach. So it is hoped that it can provide insight to the medical world about the risks to the "Suspect" and "Confirm" groups who experience an event (death).

**LITERATURE REVIEW**

Prospective study data from the number of events (event) and non-event (non-event) in two groups (table 2 x 2), can be obtained effect sizes in the form of risk ratios, risk differences, and odds ratios. This data can be represented as cells A, B, C, and D as shown in Table 1 [2].

**Table 1.** Contingency Table 2 x 2 after of Treatment

	<i>Event</i>	<i>Non-Event</i>	<i>N</i>
<i>Experiment</i>	<i>A</i>	<i>B</i>	<i>n<sub>1</sub></i>
<i>Control</i>	<i>C</i>	<i>D</i>	<i>n<sub>2</sub></i>

The estimated effect size risk ratio is based on Table 1, in each group as follows [3].

$$RiskRatio = \frac{A/n_1}{C/n_2}$$

(1)

The risk ratio calculation is converted to a log scale, both for fixed effects and random effects. The log risk ratio formula, log risk ratio variance, and standard error log risk ratio are as follows.

$$LogRiskRatio = \ln ( RiskRatio )$$

(2)

$$V_{LogRiskRatio} = \frac{1}{A} - \frac{1}{n_1} + \frac{1}{C} - \frac{1}{n_2}$$

(3)

$$SE_{LogRiskRatio} = \sqrt{V_{LogRiskRatio}}$$

(4)

Equation (5) is the formula for converting the log risk ratio into a risk ratio, while equations (6) and (7) are the confidence interval (CI) risk ratio formula after being converted from the log risk ratio.

$$RiskRatio = \exp(LogRiskRatio)$$

(5)

$$LL_{RiskRatio} = \exp(LL_{LogRiskRatio})$$

(6)

$$UL_{RiskRatio} = \exp(UL_{LogRiskRatio})$$

(7)

The size of the risk ratio can be divided into three conditions [3], (RR = 1 means the risk of the event is the same in both experimental and control groups; RR <1 means that the event risk in the experimental group is lower than the control group; RR > 1 means the event risk in the group experiment higher than the control group).

Heterogeneity identification is carried out to determine whether the effect size of the studies modeled in the meta-analysis is homogeneous or heterogeneous. The identification of heterogeneity in meta-analysis can be seen using the Q and I<sup>2</sup> statistics [14].

1. Cochran Q Homogeneity Test

H<sub>0</sub>: Effect size between homogeneous studies

H<sub>1</sub>: Effect size between heterogeneous studies

Test statistics:

$$Q = \sum_{j=1}^k w_j (T_j - \bar{T})^2$$

(8)

H<sub>0</sub> is rejected if  $Q > \chi^2_{(\alpha, k-1)}$ .

2. Calculated, I<sup>2</sup>

I<sup>2</sup> statistics are as follows [15].

$$I^2 = \begin{cases} \frac{Q - (k - 1)}{Q} \times 100\% & , \text{ if } Q > k - 1 \\ 0 & , \text{ if } Q \leq k - 1 \end{cases}$$

(9)

Interpretation I<sup>2</sup> was classified as follows (low heterogeneity (0% < I<sup>2</sup> <25%), moderate heterogeneity (26% < I<sup>2</sup> <50%), moderately high heterogeneity (51% < I<sup>2</sup> <75%), and very high heterogeneity (76% < I<sup>2</sup> <100%))

The graphic method used to visually display the meta-analysis results is a forest plot. Forest plots allow the results of all studies at a glance and provide estimated effect sizes with suitable confidence intervals [15]. In the forest plot the effects of each study and the estimated combined effects are described by plots (points) with certain confidence intervals, so that it can be seen whether the effects of each study tend to be the same or different from one study to the next. Forest plots are an important tool used to summarize information about individual studies, provide conclusions from a number of heterogeneous studies in a visual form, and show the estimated common effect results in a single image [16].

RESEARCH METHODOLOGY

The data used in this study are secondary data obtained from <https://covid19.sidoarjokab.go.id/#angka> as of 13/12/2020 at 17.00 WIB [17]. The data obtained is data on the number of “Suspect” and “Confirm” suffering from COVID-19, and dying from COVID-19 for each district in Sidoarjo Regency. Research variables include:

1. Suspected case, a person can be called a suspected COVID-19 if they have one or more of the following criteria:
  - a) Experiencing symptoms of a respiratory tract infection (ARI), such as fever or a history of fever with a temperature above 38 degrees Celsius and one of the symptoms of a respiratory disease, such as coughing, shortness of breath, sore throat, and runny nose
  - b) Have a history of contact with people who are in the probable category or have been confirmed to have COVID-19 within the last 14 days.
  - c) Suffering from a respiratory tract infection (ARI) with severe symptoms and needs to be treated in hospital without a specific cause.
2. Confirmation case, is a person who has tested positive for the Corona virus based on the results of a laboratory examination in the form of PCR. Confirmation cases can occur in people with symptoms of the Corona virus or people who have no symptoms at all.

The method of analysis in this study used meta-analysis for binary data (“Suspect” or “Confirm”) effect size risk ratio using Openmeta [analyst] Software [18]. The steps for meta analysis in this study are as follows:

- 1) Prepare data for “Suspect” and “Confirm” for COVID-19 cases in Sidoarjo Regency where “Suspect” consists of “Suspect Cured”, and “Suspect Died”, and “Confirm” consists of “recovered” and “died” data
- 2) Defining event and non-event groups for the analysis group, that is, events are defined as “Suspect” Died “for” Suspect “and” Confirm “groups, and non-event is defined as” Suspect Healed “for” Suspect “and” recovered “groups “For the” Confirm “group
- 3) Calculating the effect size, namely the district risk ratio for each analysis group in point (2)
- 4) Testing the effect size heterogeneity between district s in Sidoarjo Regency.
- 5) Predict the pessimistic, actual, and optimistic risk for point (2) where the pessimistic risk is the Upper Limit (UL) of the risk ratio and the pessimistic risk is the Lower Limit (LL) of the risk ratio. The actual prediction is the risk ratio value itself. This risk prediction is carried out for each district in Sidoarjo Regency and for Sidoarjo Regency as a whole.
- 6) Interpret the analysis results and draw conclusions

**ANALYSIS AND DISCUSSION**

Everyone with a "Suspect" and "Confirm" status has a risk of dying. However, the risk of dying from these two groups was not the same in that the risk of dying from the "Suspect" group tended to be lower than the "Confirm" group. This is because the "Confirm" group is a person who

has tested positive for the Corona virus based on the results of laboratory tests in the form of PCR, while in the "Suspect" group there is no PCR examination. Table 1 is the data for the "Suspect" and "Confirm" groups for each district in Sidoarjo Regency.

Table 1. Distribution of Covid-19 per District in Sidoarjo Regency (Monday, 26 October 2020) [17]

Districts	"Suspect"	"Suspect" Cured	"Suspect" Died	Percentage of "Suspect" Died	"Confirm"	"Confirm" Cured	"Confirm" Died	Percentage of "Confirm" Died
Sidoarjo	1404	1324	4	0.285	975	914	55	5.641
Buduran	306	252	4	1.307	415	385	21	5.060
Candi	200	193	5	2.500	546	488	33	6.044
Gedangan	228	208	8	3.509	515	481	28	5.437
Tanggulangin	139	115	12	8.633	282	263	18	6.383
Porong	97	97	2	2.062	205	185	9	4.390
Jabon	94	87	0	0.000	111	90	16	14.414
Taman	377	373	7	1.857	921	846	54	5.863
Krembung	204	178	1	0.490	169	156	12	7.101
Wonoayu	90	88	3	3.333	202	179	9	4.455
Tulangan	176	172	1	0.568	368	337	17	4.620
Krian	207	197	0	0.000	398	334	34	8.543
Prambon	120	112	6	5.000	158	136	10	6.329
Sukodono	157	138	12	7.643	350	306	25	7.143
Sedati	102	92	2	1.961	321	298	23	7.165
Waru	309	287	6	1.942	895	825	69	7.709
Balombang	88	87	7	7.955	183	163	20	10.929
Tarik	56	53	2	3.571	101	80	12	11.881
Total	4354		82	1.883	7115		465	6.535

Source: <https://covid19.sidoarjokab.go.id/#angka>

Table 1 shows that globally 1.883% (82/4354) people from the "Suspect" group died, while 6.535% (465/7115) people from the "Confirm" group died. This percentage indicates that people in the "Confirm" group had a greater risk of dying than people in the "Suspect" group. Meanwhile, Tanggulangin and Sukodono districts gave a greater risk of dying in the "Suspect" group than in the

"Confirm" group, which were respectively 8.633% (12/139) and 6.383% (18/282) in Tanggulangin district, while in districts Sukodono was 7.643% (12/157) for the "Suspect" group and 7.165% (23/321) for the "Confirm" group. Furthermore, the heterogeneity test, which is more detailed is presented in the following table.

Table 2. Heterogeneity Test

Heterogeneity	tau^2	Q(df=17)	Het. p-Value	I^2
Value	0.608	54.358	< 0.001	68.726

Table 2 shows that the effect size between districts in Sidoarjo Regency is heterogeneous as indicated by Het. p-value of <0.001 (less than 0.05). The value of I<sup>2</sup> = 68.726 indicates that the heterogeneity is quite high because the value lies in the interval of 51% < I<sup>2</sup> < 75%. The foregoing states that the model used is random effects, and the results are presented in the following table.

Table 3. Results of the Random Effects Model

Random Effects Model	Estimate	Lower bound	Upper bound	p-Value
Value	0.357	0.225	0.567	< 0.001

The results of testing the relationship between the "Suspect" and "Confirm" groups with death events were significant, indicated by a p-Value <0.001. Estimate (RR = 0.357, 95% CI (0.225; 0.567) shows that people in the "Suspect" group in Sidoarjo Regency have a risk of death 0.357 than people in the "Confirm" group. If people in the "Suspect" group have a worse health condition from the actual, the pessimistic risk prediction is 0.567, meaning

that people in the "Suspect" group in Sidoarjo Regency have a risk of dying 0.567 times greater than people in the "Confirm" group. Furthermore, if people in the "Suspect" group have a better health condition from the actual, the optimistic risk prediction is 0.225, meaning that people in the "Suspect" group in Sidoarjo Regency have a risk of dying of 0.225 compared to people in the "Confirm" group. in the following table.

Table 4. Prediction of Relative Risk for "Suspect" and "Confirm" groups per District in Sidoarjo Regency

District	Relative Risk			
	Actual	optimistic	pessimistic	p-value
Sidoarjo	0.051	0.018	0.139	0.000
Buduran	0.258	0.090	0.745	0.008
Candi	0.414	0.164	1.045	0.007
Gedangan	0.645	0.299	1.394	0.012
Tanggulangin	1.353	0.671	2.728	0.056
Porong	0.470	0.103	2.132	0.037
Jabon	0.036	0.002	0.588	0.014
Taman	0.317	0.145	0.690	0.004
Krembung	0.069	0.009	0.526	0.001
Wonoayu	0.748	0.207	2.698	0.001
Tulangan	0.123	0.017	0.917	<0.001
Krian	0.028	0.002	0.451	<0.001
Prambon	0.790	0.295	2.113	<0.001
Sukodono	1.070	0.552	2.075	<0.001
Sedati	0.274	0.066	1.141	<0.001
Waru	0.252	0.110	0.574	<0.001
Balongsendo	0.728	0.320	1.656	<0.001
Tarik	0.301	0.070	1.296	<0.001

Table 4, which is an individual model, shows that the prediction of actual relative risk is obtained by a confidence interval of 95% (0.253; 0.628). So that based on the results of the prediction of the actual relative risk, the "Suspect" and "Confirm" groups can be divided into 3 zones, namely Zone 1, the relative risk is less than 0.253; Zone 2 relative risk between 0.253 to 0.628; and Zone 3 relative risk is more than 0.628. Thus Zone 1 is in Sidoarjo district, Jabon district, Krembung district, Tulangan district, Krian district and Waru district. Zone 2 is in Buduran district, Candi district, Porong district, Taman district, Sedati district, and Tarik district. Furthermore,

Zone 3 is in Gedangan district, Tanggulangin district, Wonoayu district, Prambon district, Sukodono district, and Balongsendo district. Especially in Zone 3, Tanggulangin district gives a p-value of 0.056 which is greater than  $\alpha = 0.05$ , so it can be said that the relative risk prediction of the "Suspect" and "Confirm" groups is not significant.

For simultaneous modeling, it can be seen through the forest plot. The forest plot of the relationship between the "Suspect" and "Confirm" groups and the death event due to COVID-19 in Sidoarjo Regency is shown in Figure 1.

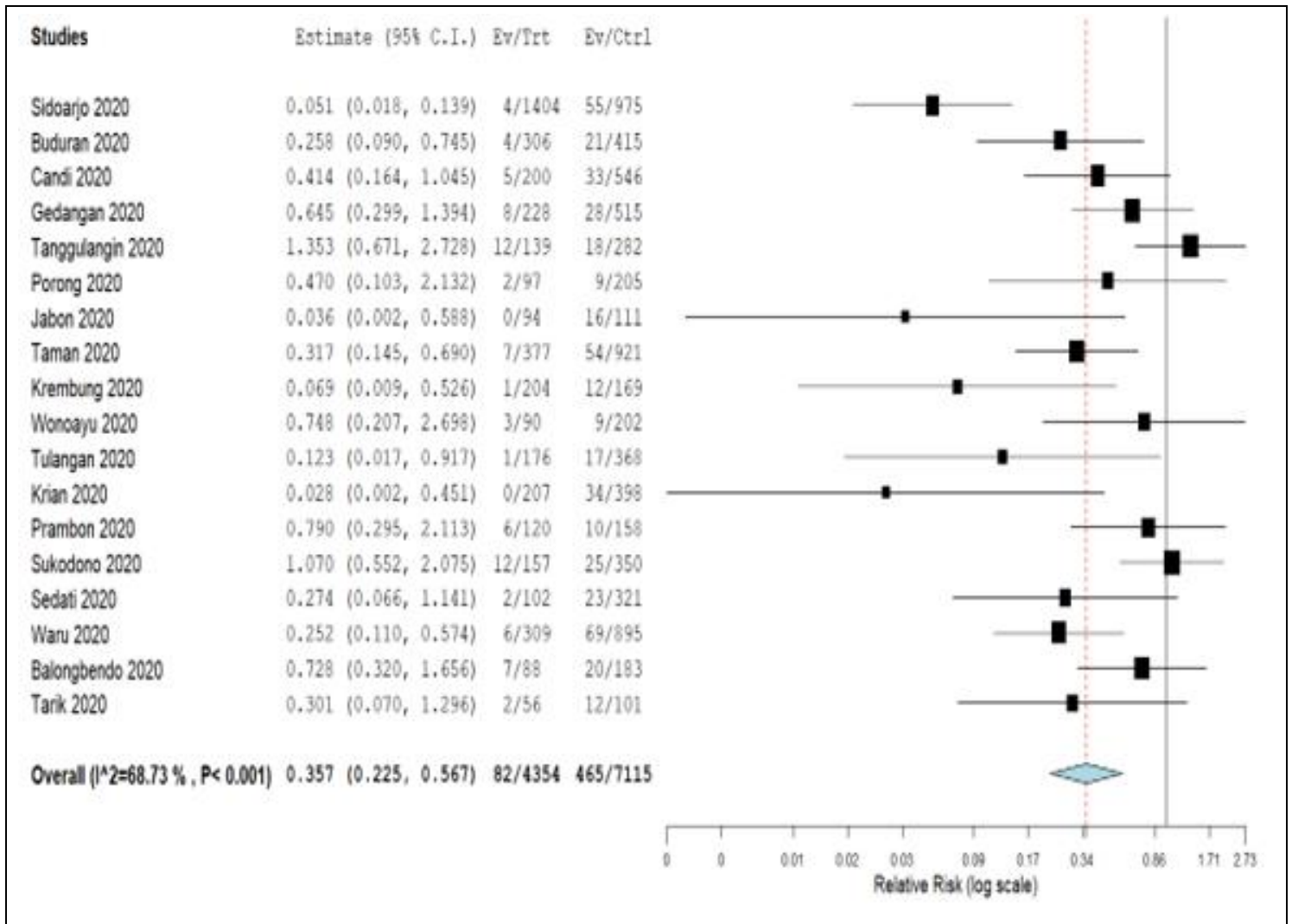


Figure 1. Forest Plot Relative Risk (log scale) of "Suspect" and "Confirm" Groups Died

Figure 1 shows that the relative risk groups can be grouped into 3 parts. Group 1 consists of a relative risk of less than 0.225, namely Sidoarjo District (0.051), Jabon District (0.036), Kremlung District (0.069), Tulangan District (0.123), and Krian District (0.028). Group 2 consists of relative risks from 0.225 to 0.567, namely Buduran District (0.258), Candi District (0.414), Porong District (0.470), Taman District (0.317), Sedati District (0.274), Waru District (0.252), and District Districts. Withdraw (0.301). Group 3 consists of risks above 0.567, namely Gedangan District (0.645), Tanggulangin District (1.353), Wonoayu District (0.748), Prambon District (0.790), Sukodono District (1.070), and Balongsendo District (0.728). If it is based on Relative Risk (log scale) Group 1 consists of Sidoarjo district, Buduran district, Jabon district, Taman district, Kremlung district, Tulangan district, Krian district, Sedati district, Waru district, and Tarik district. Group 2 consists of Candi district, Gedangan district, Porong district, Wonoayu district, Prambon district and Balongsendo district. Meanwhile, group 3 has 2 district s, namely Tanggulangin district and Sukodono district.

The results from Table 4 and Figure 1 show that the optimistic prediction, namely the lowest relative risk of death in the "Suspect" and "Confirm" Covid-19 groups is in Krian sub-district (0.002), Jabon sub-district (0.002), Kremlung district (0.009) and sub-district. Sidoarjo (0.018). While the pessimistic prediction, namely the

highest relative risk of death in the "Suspect" and "Confirm" Covid-19 groups is in Tanggulangin sub-district (2,728), Porong sub-district (2,132), Wonoayu sub-district (2,698), and Prambon sub-district (2,133), Sukodono district. (2,075). This can happen to people with symptoms of the Corona virus or people who have no symptoms at all.

**CONCLUSION**

The "Confirm" group or people who have tested positive for the Corona virus based on the results of laboratory tests in the form of PCR have a greater risk of dying than the "Suspect" group. The districts in Sidoarjo Regency with the highest risk of dying in confirmed cases are Tanggulangin District, Wonoayu District, Prambon District, Sukodono District. While the lowest relative risk of dying was in Krian district, Jabon district, Kremlung district and Sidoarjo district.

**CONFLICTS OF INTEREST**

The authors declare that there are no conflicts of interest regarding the publication of this paper

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