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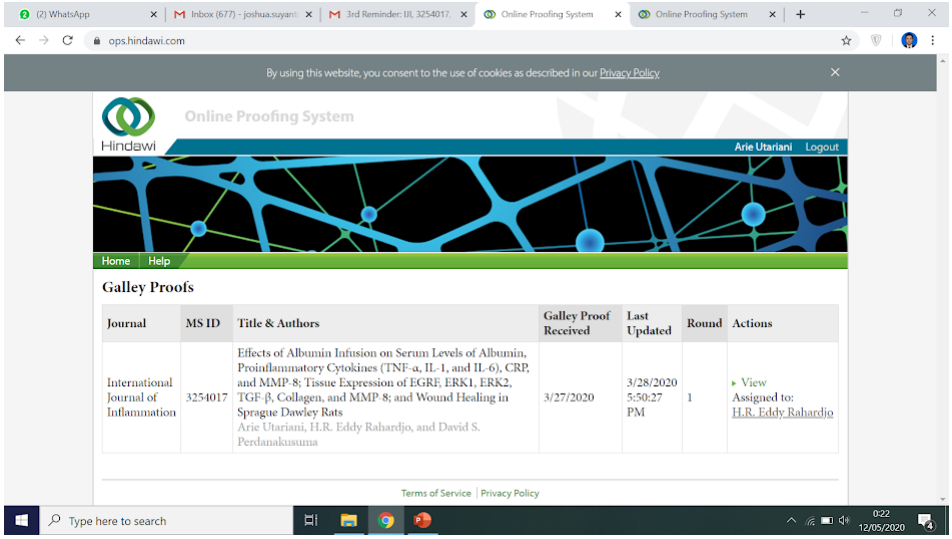


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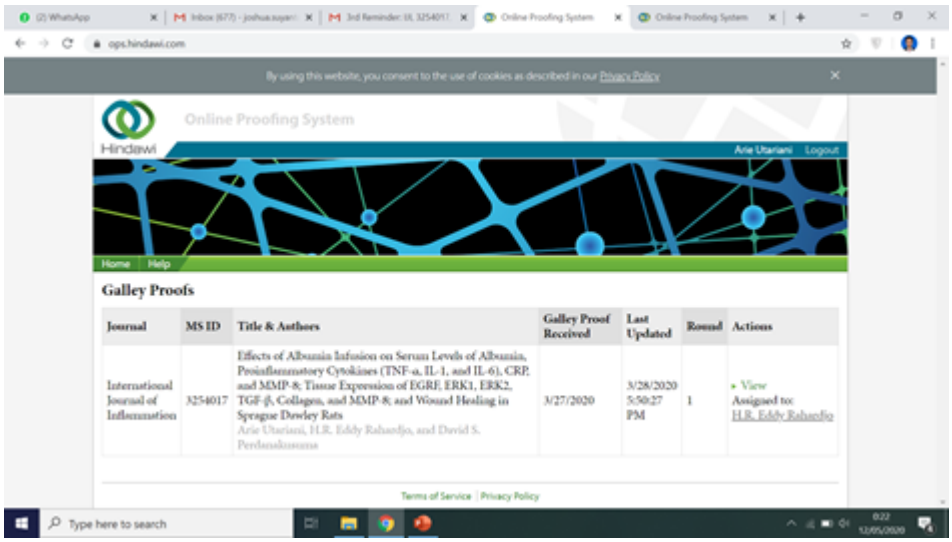


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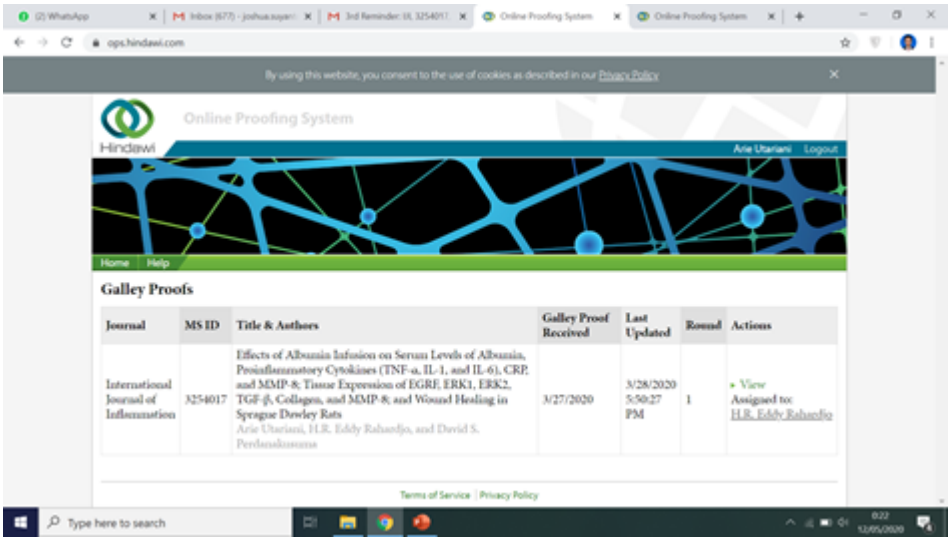


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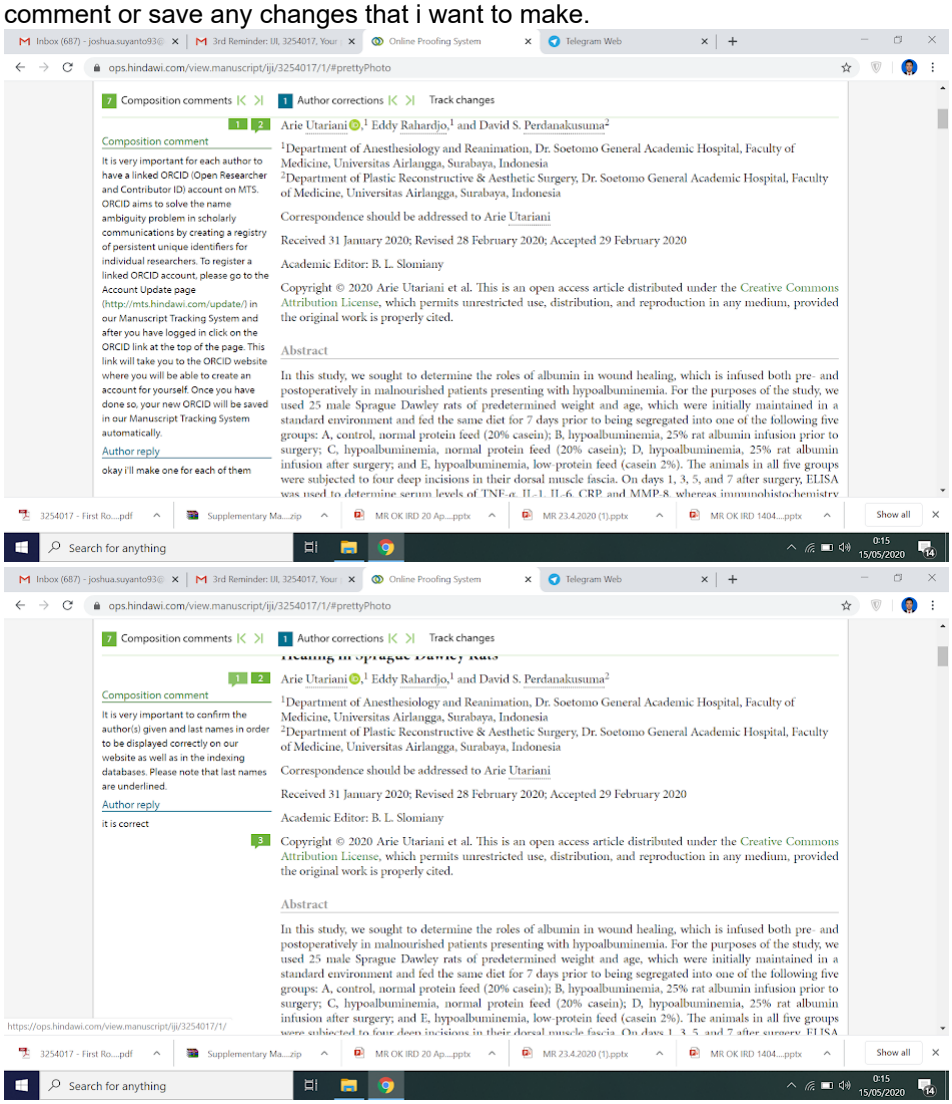

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Research Article

# Effects of Albumin Infusion on Serum Levels of Albumin, Proinflammatory Cytokines (TNF-α, IL-1, and IL-6), CRP, and MMP-8; Tissue Expression of EGRF, ERK1, ERK2, TGF-β, Collagen, and MMP-8; and Wound Healing in Sprague Dawley Rats

Arie Utariani,[1] Eddy Rahardjo,[1] and David S. Perdanakusuma[2]

[1]Department of Anesthesiology and Reanimation, Dr. Soetomo General Academic Hospital, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[2]Department of Plastic Reconstructive & Aesthetic Surgery, Dr. Soetomo General Academic Hospital, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

Correspondence should be addressed to Arie Utariani

Received 31 January 2020; Revised 28 February 2020; Accepted 29 February 2020

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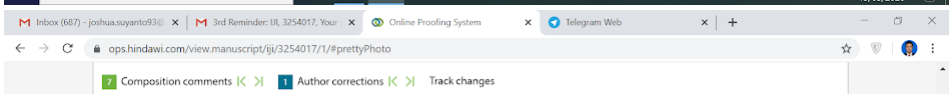

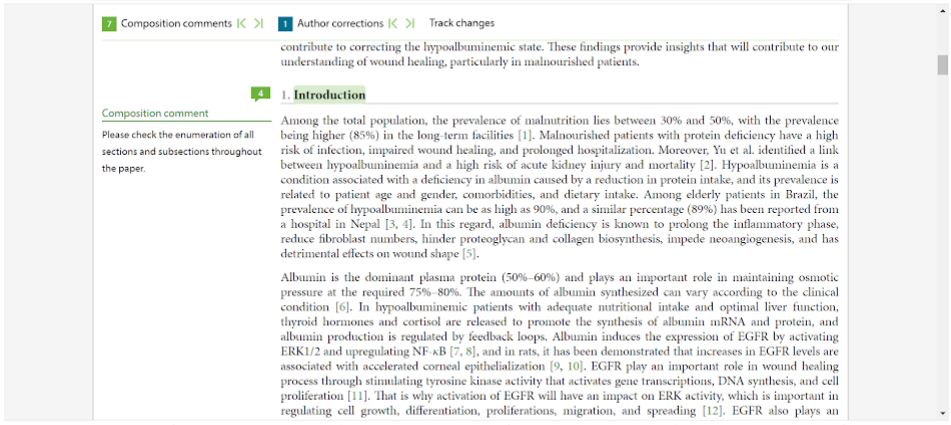

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contribute to correcting the hypoalbuminemic state. These findings provide insights that will contribute to our understanding of wound healing, particularly in malnourished patients.

## 1. Introduction

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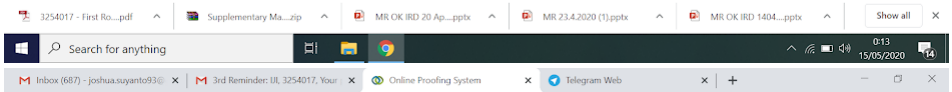
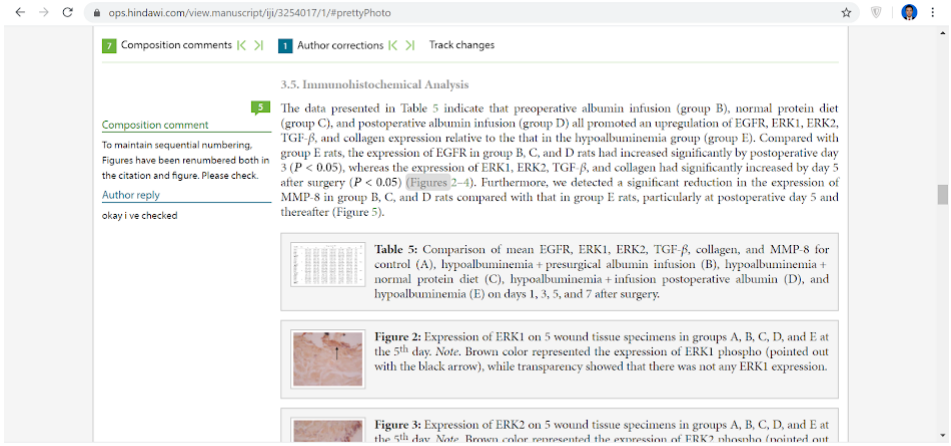
Among the total population, the prevalence of malnutrition lies between 30% and 50%, with the prevalence being higher (85%) in the long-term facilities [1]. Malnourished patients with protein deficiency have a high risk of infection, impaired wound healing, and prolonged hospitalization. Moreover, Yu et al. identified a link between hypoalbuminemia and a high risk of acute kidney injury and mortality [2]. Hypoalbuminemia is a condition associated with a deficiency in albumin caused by a reduction in protein intake, and its prevalence is related to patient age and gender, comorbidities, and dietary intake. Among elderly patients in Brazil, the prevalence of hypoalbuminemia can be as high as 90%, and a similar percentage (89%) has been reported from a hospital in Nepal [3, 4]. In this regard, albumin deficiency is known to prolong the inflammatory phase, reduce fibroblast numbers, hinder proteoglycan and collagen biosynthesis, impede neoangiogenesis, and has detrimental effects on wound shape [5].

Albumin is the dominant plasma protein (50%–60%) and plays an important role in maintaining osmotic pressure at the required 75%–80%. The amounts of albumin synthesized can vary according to the clinical condition [6]. In hypoalbuminemic patients with adequate nutritional intake and optimal liver function, thyroid hormones and cortisol are released to promote the synthesis of albumin mRNA and protein, and albumin production is regulated by feedback loops. Albumin induces the expression of EGFR by activating ERK1/2 and upregulating NF-κB [7, 8], and in rats, it has been demonstrated that increases in EGFR levels are associated with accelerated corneal epithelialization [9, 10]. EGFR play an important role in wound healing process through stimulating tyrosine kinase activity that activates gene transcriptions, DNA synthesis, and cell proliferation [11]. That is why activation of EGFR will have an impact on ERK activity, which is important in regulating cell growth, differentiation, proliferations, migration, and spreading [12]. EGFR also plays an







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### 3.5. Immunohistochemical Analysis

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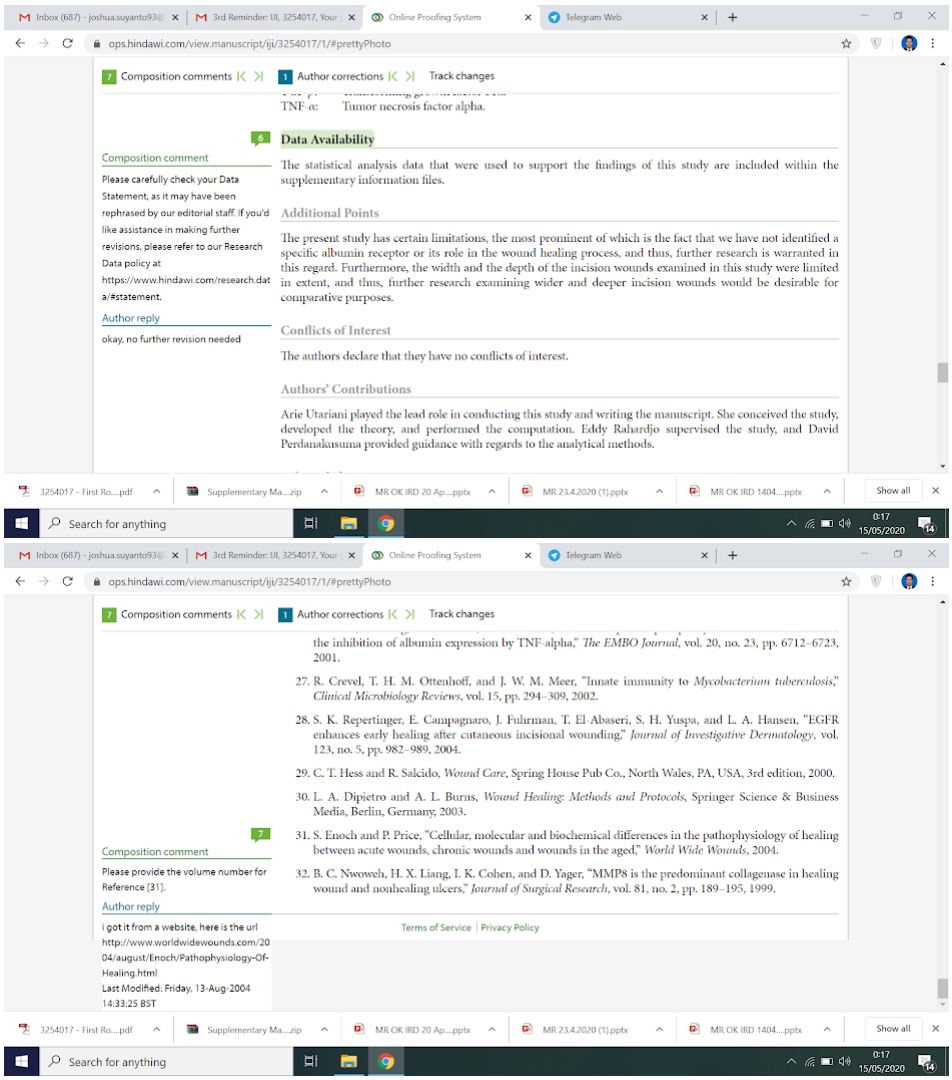
The data presented in Table 5 indicate that preoperative albumin infusion (group B), normal protein diet (group C), and postoperative albumin infusion (group D) all promoted an upregulation of EGFR, ERK1, ERK2, TGF-β, and collagen expression relative to the that in the hypoalbuminemia group (group E). Compared with group E rats, the expression of EGFR in group B, C, and D rats had increased significantly by postoperative day 3 ($P < 0.05$), whereas the expression of ERK1, ERK2, TGF-β, and collagen had significantly increased by day 5 after surgery ($P < 0.05$) (Figures 2–4). Furthermore, we detected a significant reduction in the expression of MMP-8 in group B, C, and D rats compared with that in group E rats, particularly at postoperative day 5 and thereafter (Figure 5).

**Table 5:** Comparison of mean EGFR, ERK1, ERK2, TGF-β, collagen, and MMP-8 for control (A), hypoalbuminemia + presurgical albumin infusion (B), hypoalbuminemia + normal protein diet (C), hypoalbuminemia + infusion postoperative albumin (D), and hypoalbuminemia (E) on days 1, 3, 5, and 7 after surgery.

**Figure 2:** Expression of ERK1 on 5 wound tissue specimens in groups A, B, C, D, and E at the 5th day. *Note.* Brown color represented the expression of ERK1 phospho (pointed out with the black arrow), while transparency showed that there was not any ERK1 expression.

**Figure 3:** Expression of ERK2 on 5 wound tissue specimens in groups A, B, C, D, and E at the 5th day. *Note.* Brown color represented the expression of ERK2 phospho (pointed out







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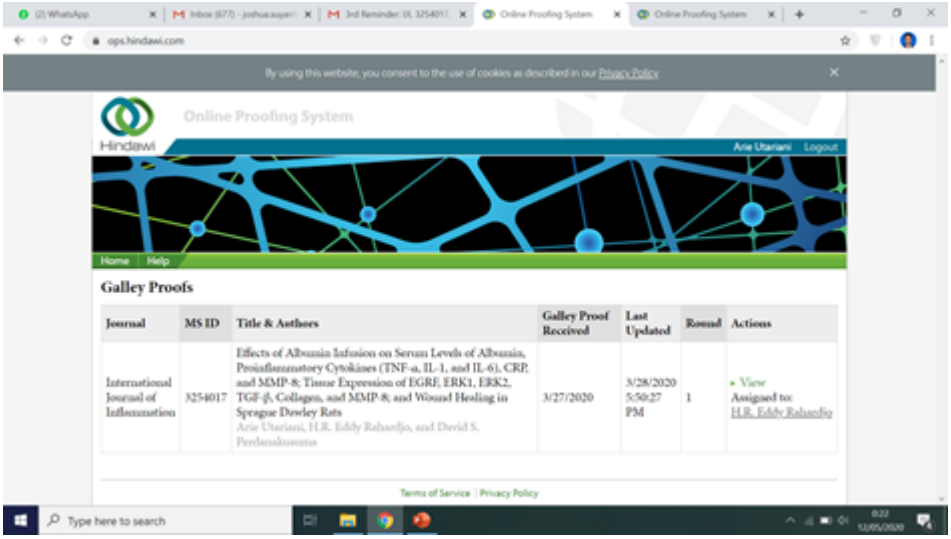


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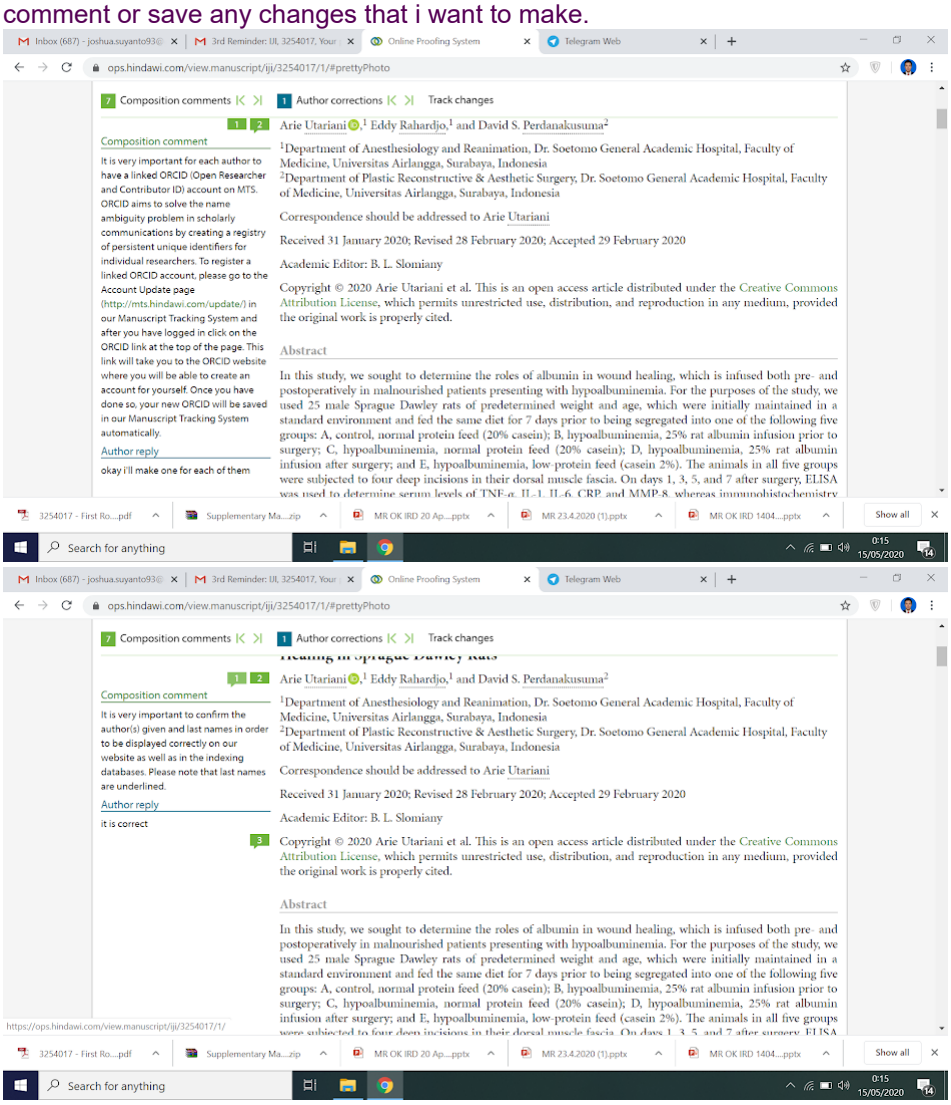

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Arie Utariani,[1] Eddy Rahardjo,[1] and David S. Perdanakusuma[2]

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[2]Department of Plastic Reconstructive & Aesthetic Surgery, Dr. Soetomo General Academic Hospital, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

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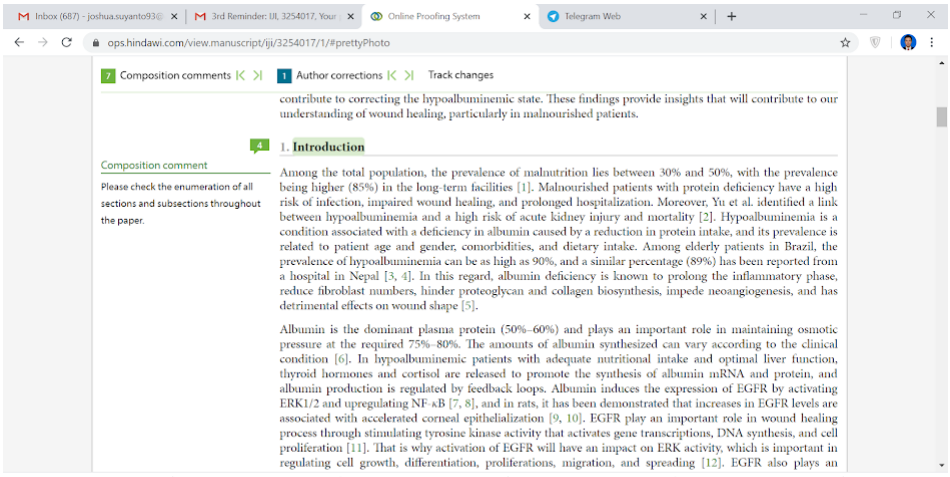

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## 1. Introduction

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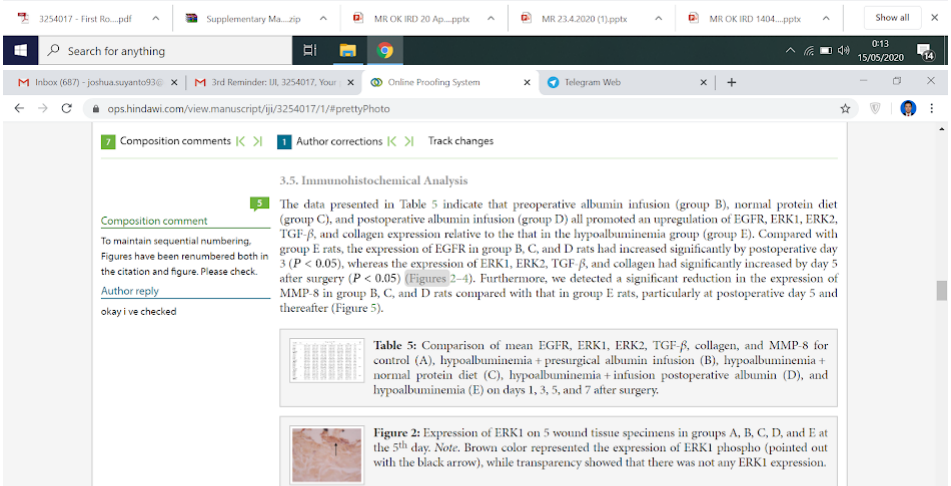

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### 3.5. Immunohistochemical Analysis

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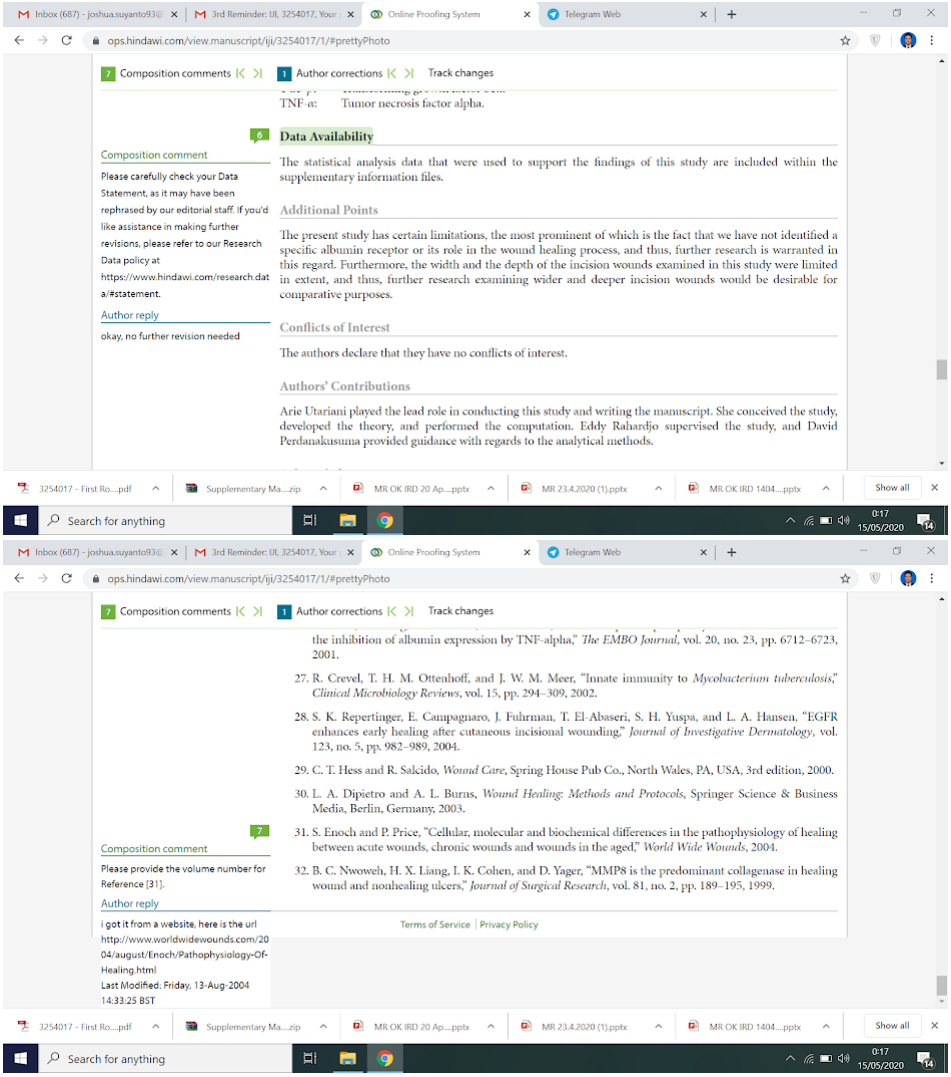
The data presented in Table 5 indicate that preoperative albumin infusion (group B), normal protein diet (group C), and postoperative albumin infusion (group D) all promoted an upregulation of EGFR, ERK1, ERK2, TGF-β, and collagen expression relative to the that in the hypoalbuminemia group (group E). Compared with group E rats, the expression of EGFR in group B, C, and D rats had increased significantly by postoperative day 3 ($P < 0.05$), whereas the expression of ERK1, ERK2, TGF-β, and collagen had significantly increased by day 5 after surgery ($P < 0.05$) (Figures 2–4). Furthermore, we detected a significant reduction in the expression of MMP-8 in group B, C, and D rats compared with that in group E rats, particularly at postoperative day 5 and thereafter (Figure 5).

**Table 5:** Comparison of mean EGFR, ERK1, ERK2, TGF-β, collagen, and MMP-8 for control (A), hypoalbuminemia + presurgical albumin infusion (B), hypoalbuminemia + normal protein diet (C), hypoalbuminemia + infusion postoperative albumin (D), and hypoalbuminemia (E) on days 1, 3, 5, and 7 after surgery.

**Figure 2:** Expression of ERK1 on 5 wound tissue specimens in groups A, B, C, D, and E at the 5th day. *Note*. Brown color represented the expression of ERK1 phospho (pointed out with the black arrow), while transparency showed that there was not any ERK1 expression.

**Figure 3:** Expression of ERK2 on 5 wound tissue specimens in groups A, B, C, D, and E at the 5th day. *Note*. Brown color represented the expression of ERK2 phospho (pointed out







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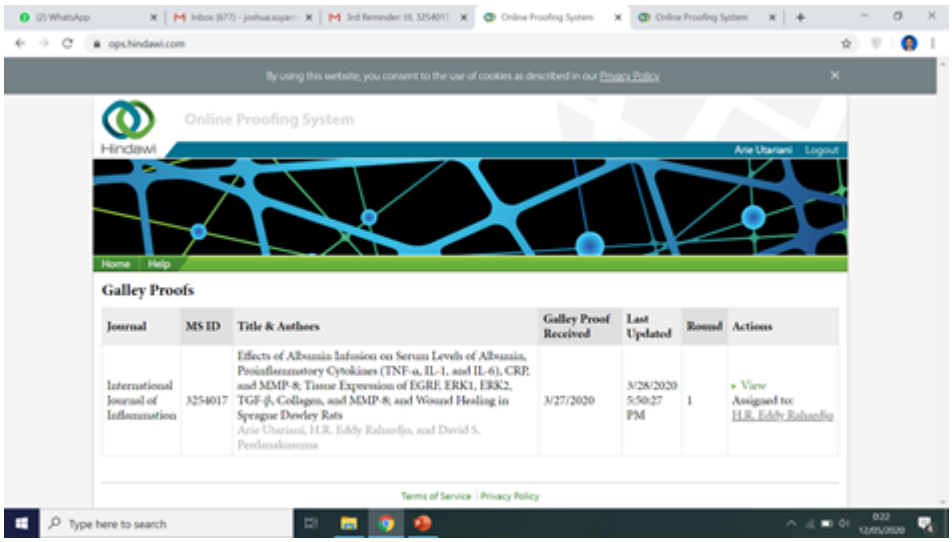


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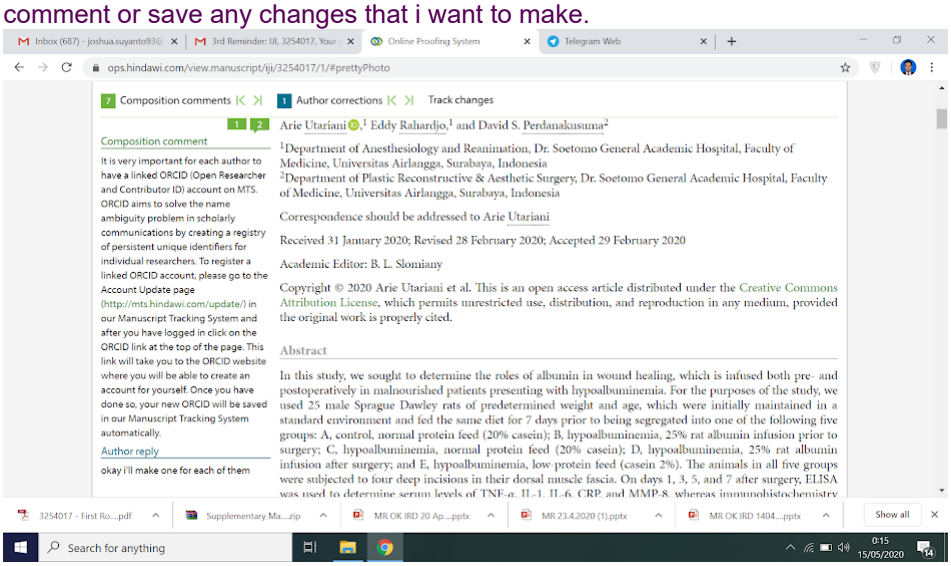

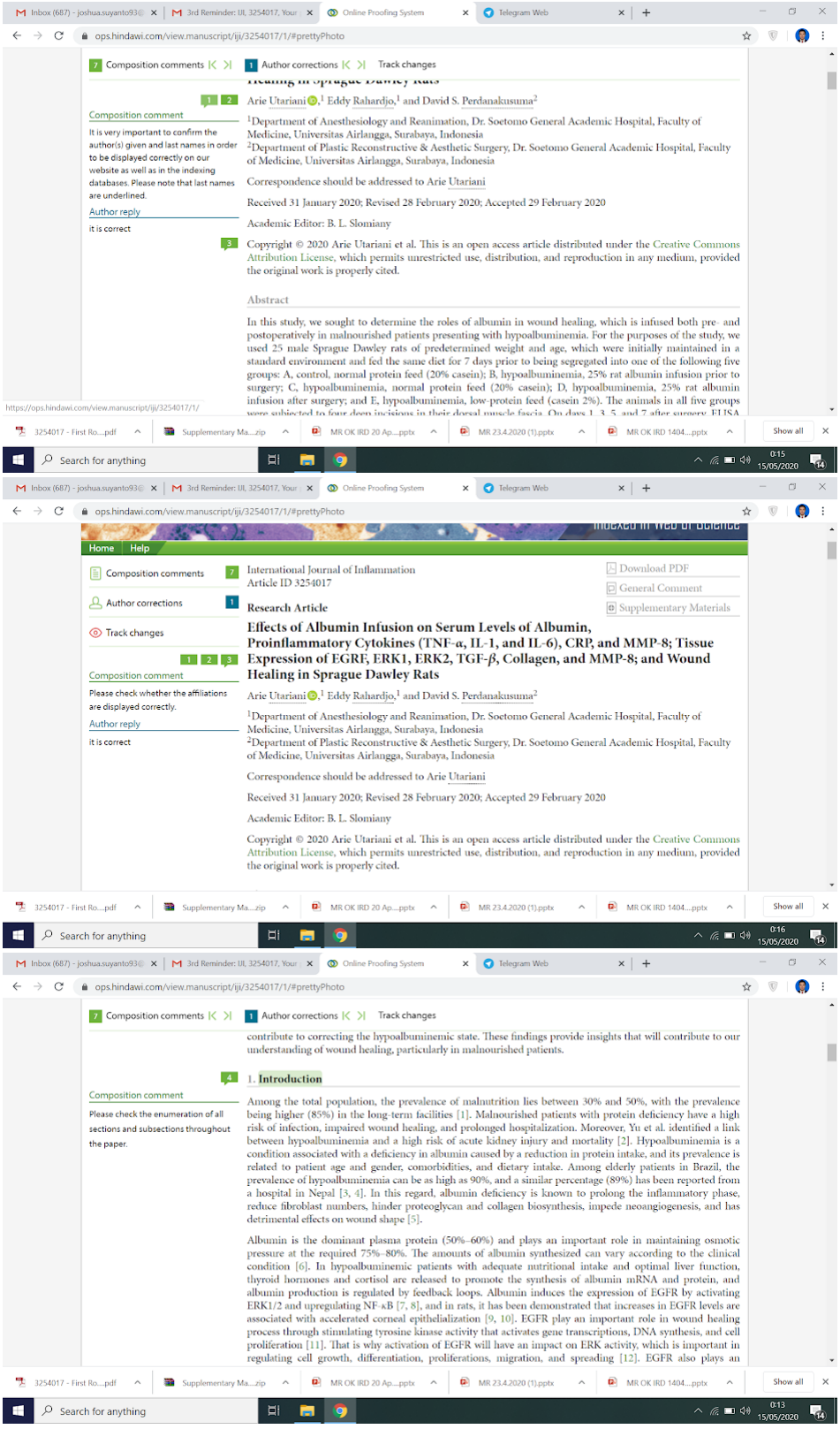

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contribute to correcting the hypoalbuminemic state. These findings provide insights that will contribute to our understanding of wound healing, particularly in malnourished patients.

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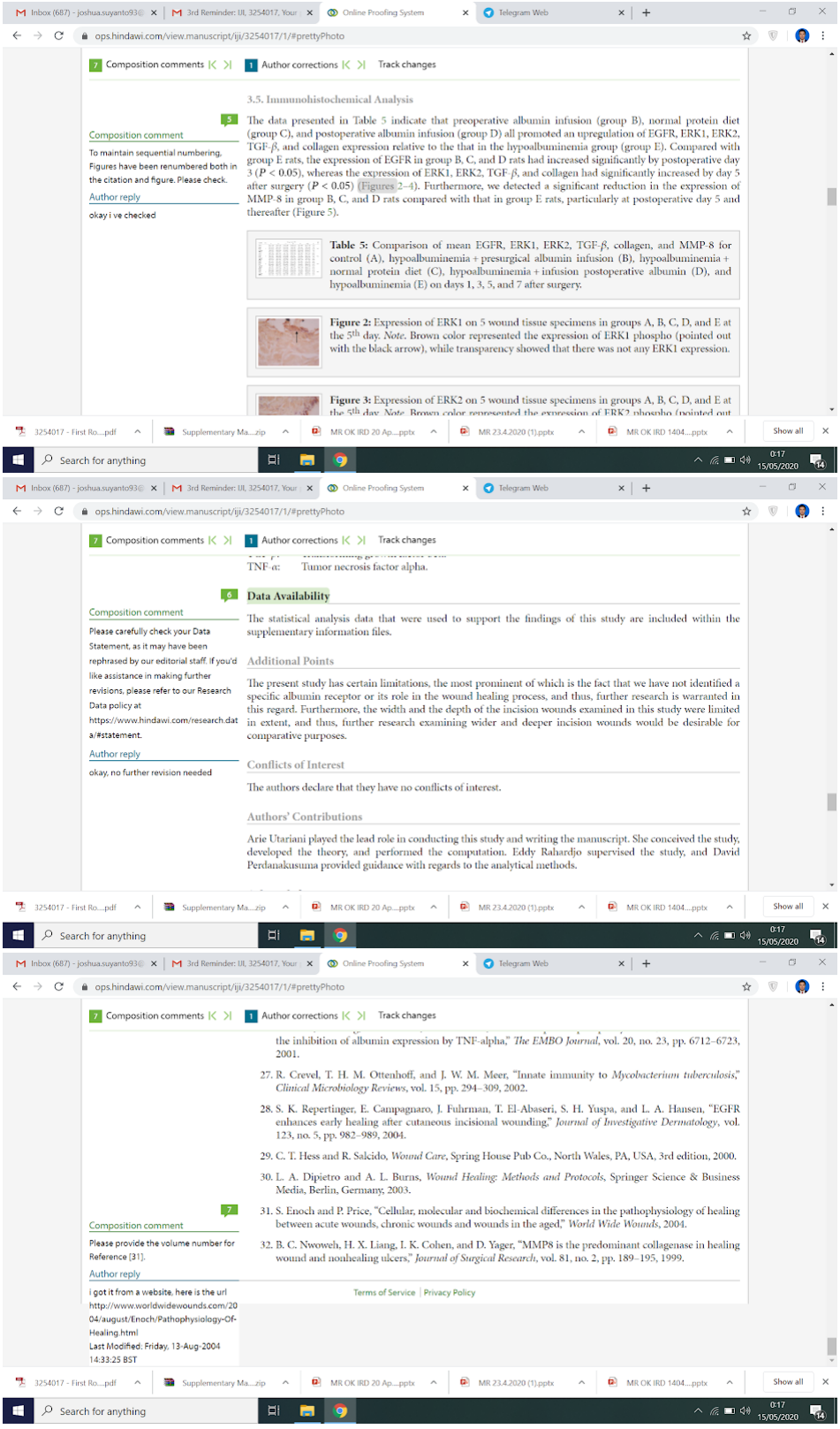


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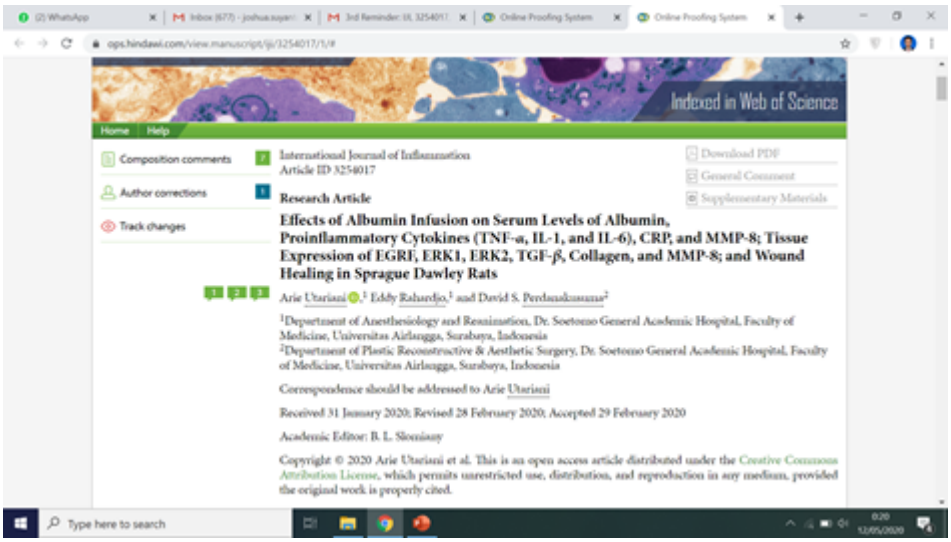


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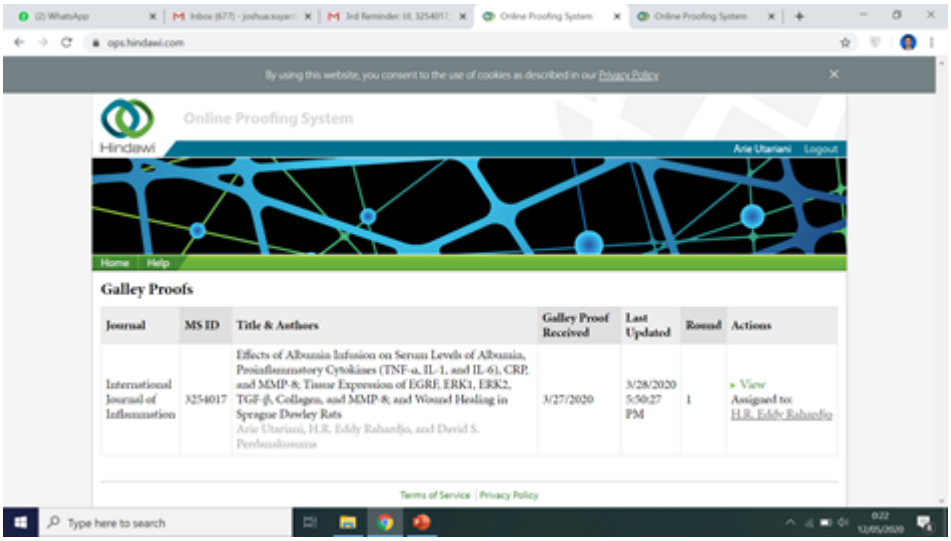


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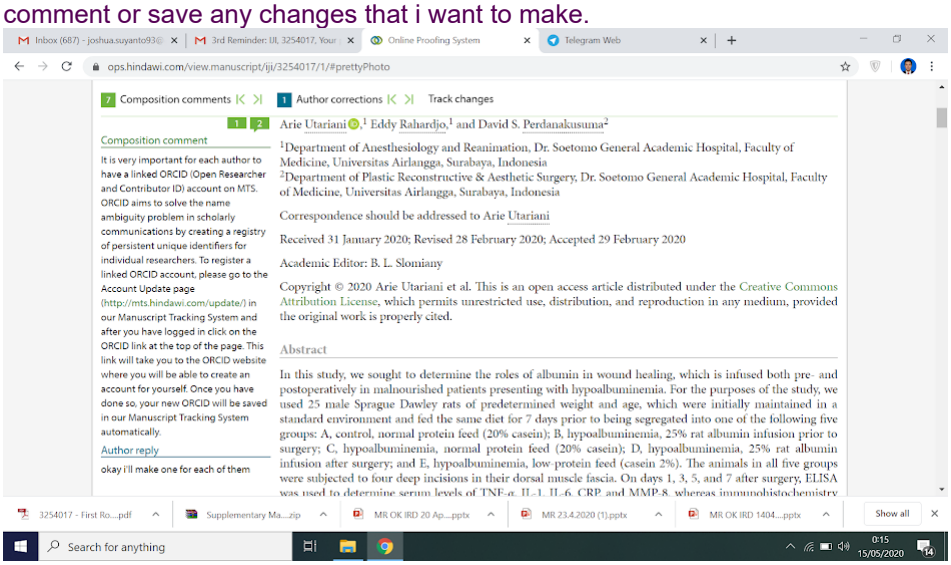

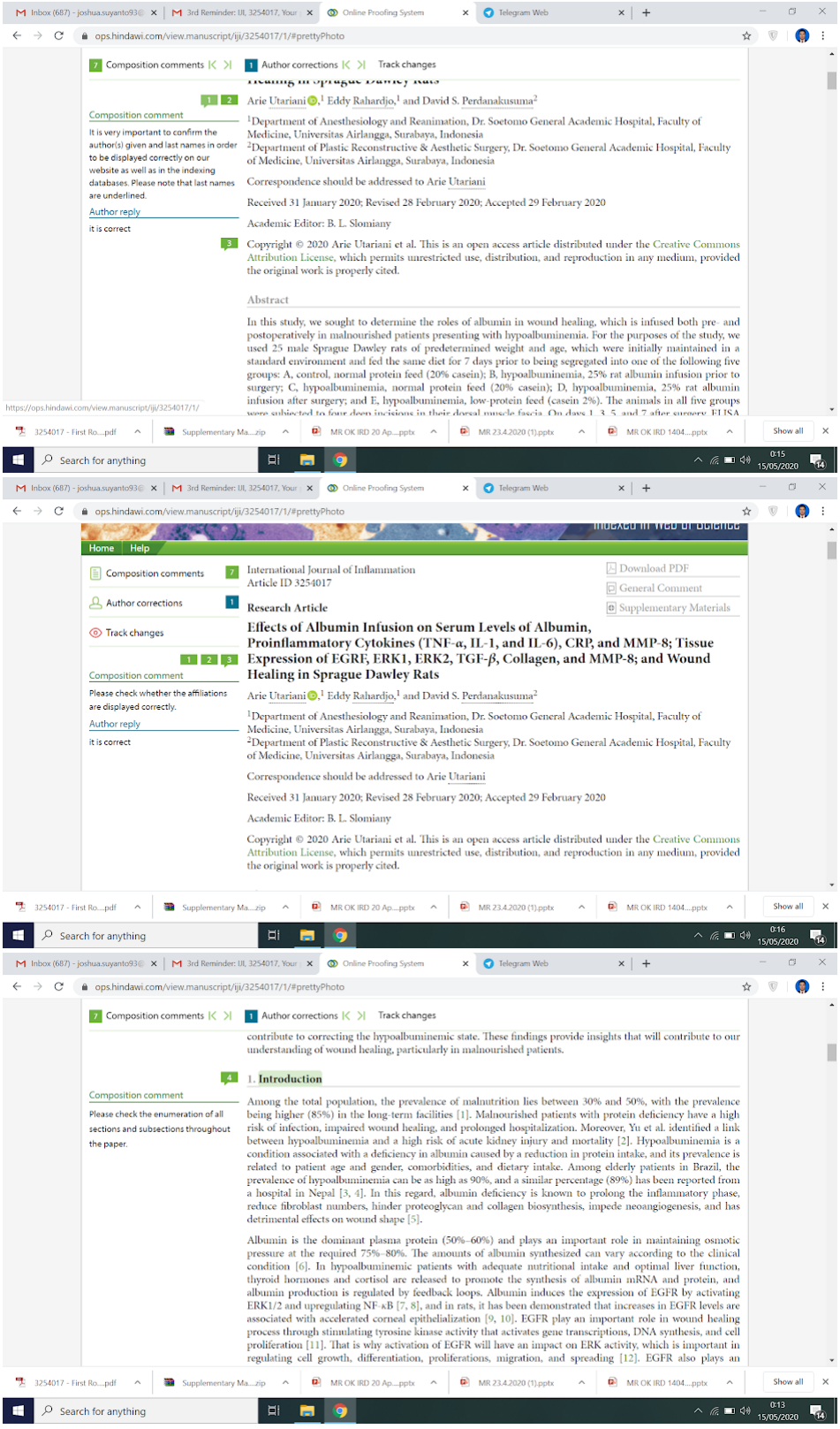

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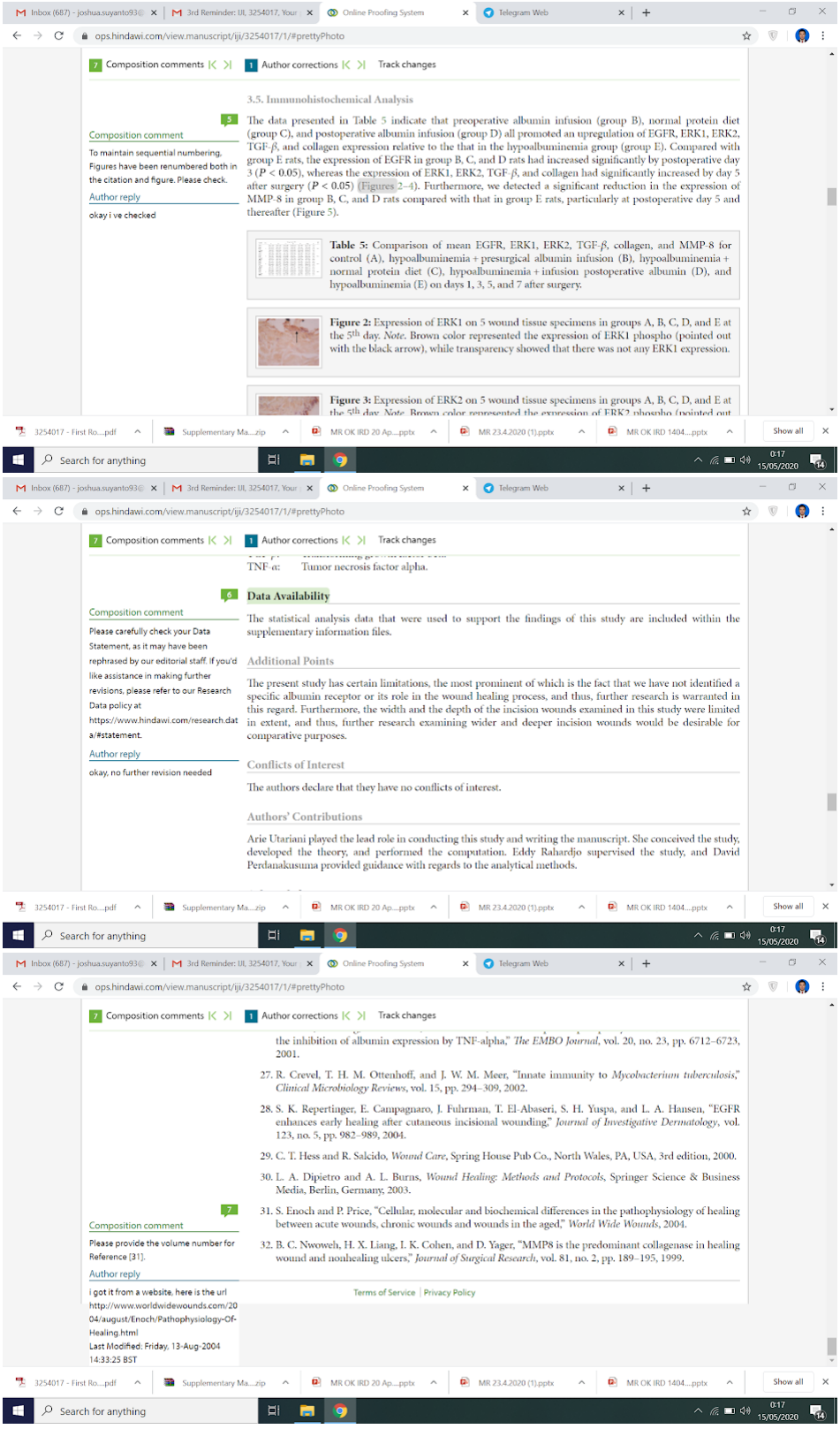


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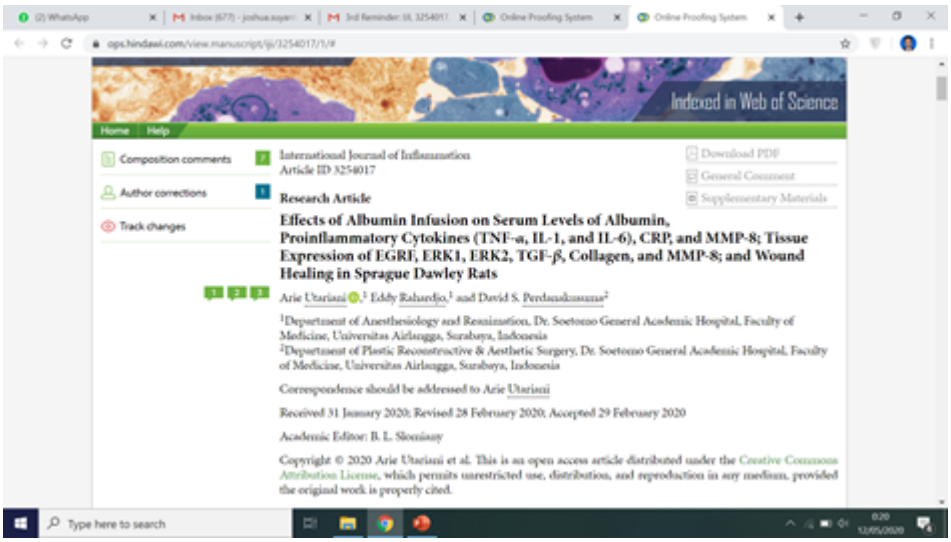


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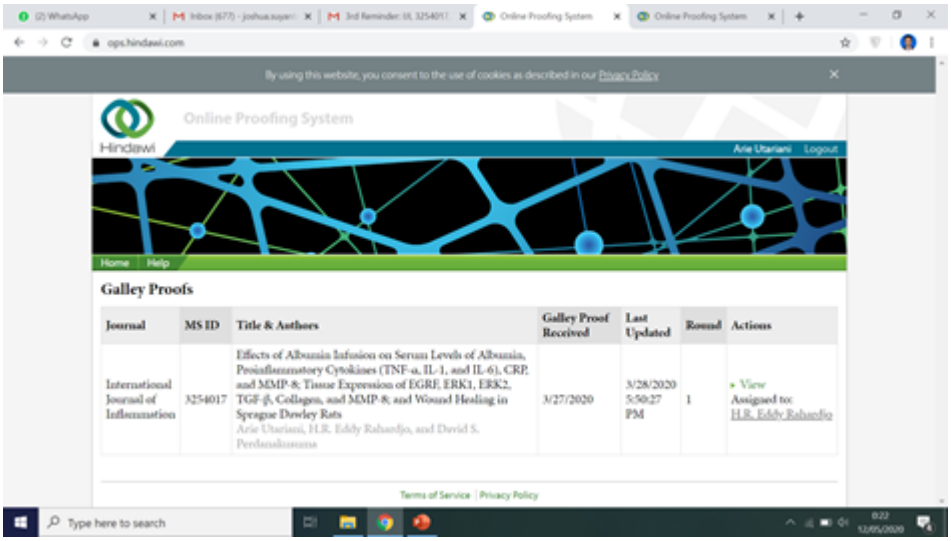


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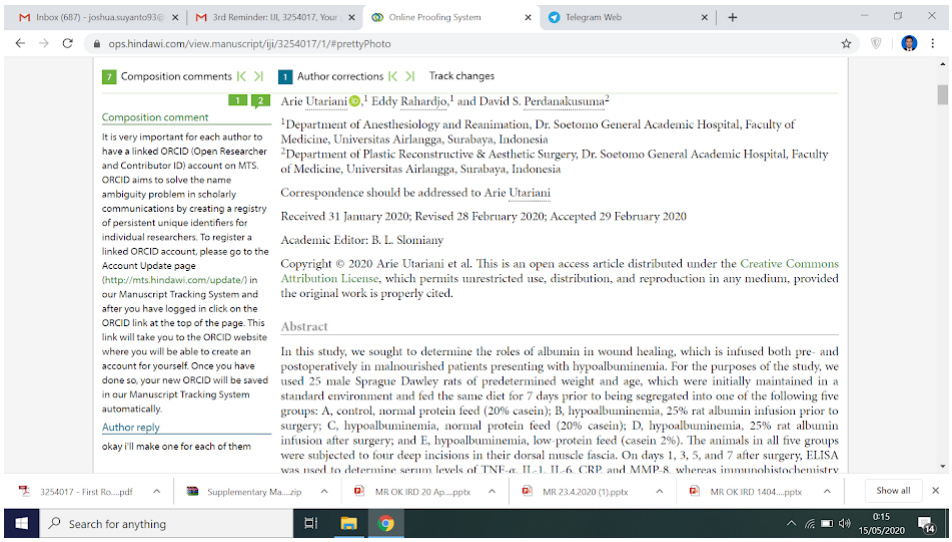

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Author reply

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Arie Utariani,[1] Eddy Rahardjo,[1] and David S. Perdanakusuma[2]

[1]Department of Anesthesiology and Reanimation, Dr. Soetomo General Academic Hospital, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[2]Department of Plastic Reconstructive & Aesthetic Surgery, Dr. Soetomo General Academic Hospital, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

Correspondence should be addressed to Arie Utariani

Received 31 January 2020; Revised 28 February 2020; Accepted 29 February 2020

Academic Editor: B. L. Slomiany



Abstract

In this study, we sought to determine the roles of albumin in wound healing, which is infused both pre- and postoperatively in malnourished patients presenting with hypoalbuminemia. For the purposes of the study, we used 25 male Sprague Dawley rats of predetermined weight and age, which were initially maintained in a standard environment and fed the same diet for 7 days prior to being segregated into one of the following five groups: A, control, normal protein feed (20% casein); B, hypoalbuminemia, 25% rat albumin infusion prior to surgery; C, hypoalbuminemia, normal protein feed (20% casein); D, hypoalbuminemia, 25% rat albumin infusion after surgery; and E, hypoalbuminemia, low-protein feed (casein 2%). The animals in all five groups were subjected to four deep incisions in their dorsal muscle fascia. On days 1, 3, 5, and 7 after surgery, ELISA was used to determine serum levels of TNF-α, IL-1, IL-6, CRP, and MMP-8, whereas immunohistochemistry

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[1]Department of Anesthesiology and Reanimation, Dr. Soetomo General Academic Hospital, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
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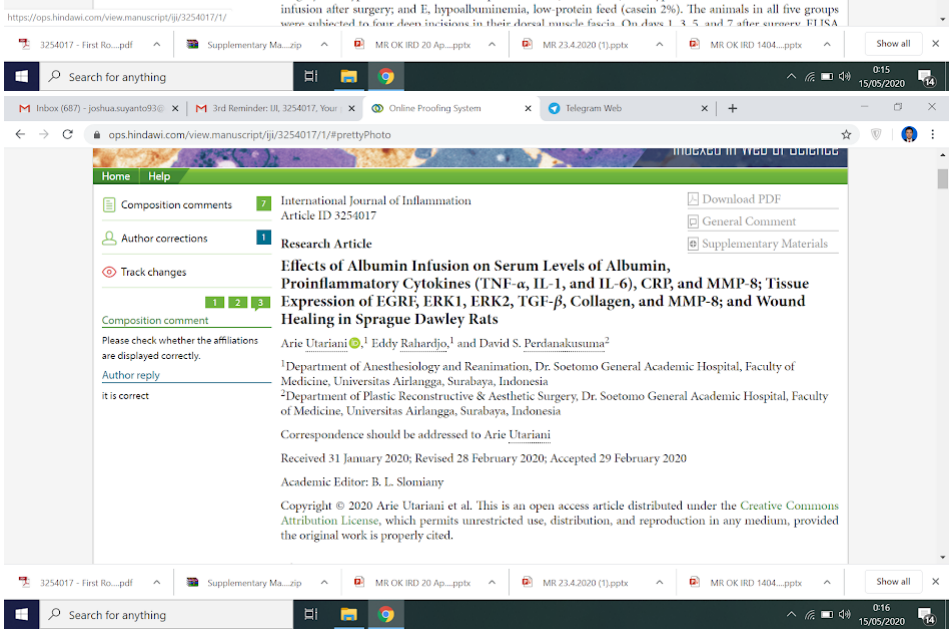

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International Journal of Inflammation
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Research Article

# Effects of Albumin Infusion on Serum Levels of Albumin, Proinflammatory Cytokines (TNF-α, IL-1, and IL-6), CRP, and MMP-8; Tissue Expression of EGRF, ERK1, ERK2, TGF-β, Collagen, and MMP-8; and Wound Healing in Sprague Dawley Rats

Arie Utariani,[1] Eddy Rahardjo,[1] and David S. Perdanakusuma[2]

[1]Department of Anesthesiology and Reanimation, Dr. Soetomo General Academic Hospital, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[2]Department of Plastic Reconstructive & Aesthetic Surgery, Dr. Soetomo General Academic Hospital, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

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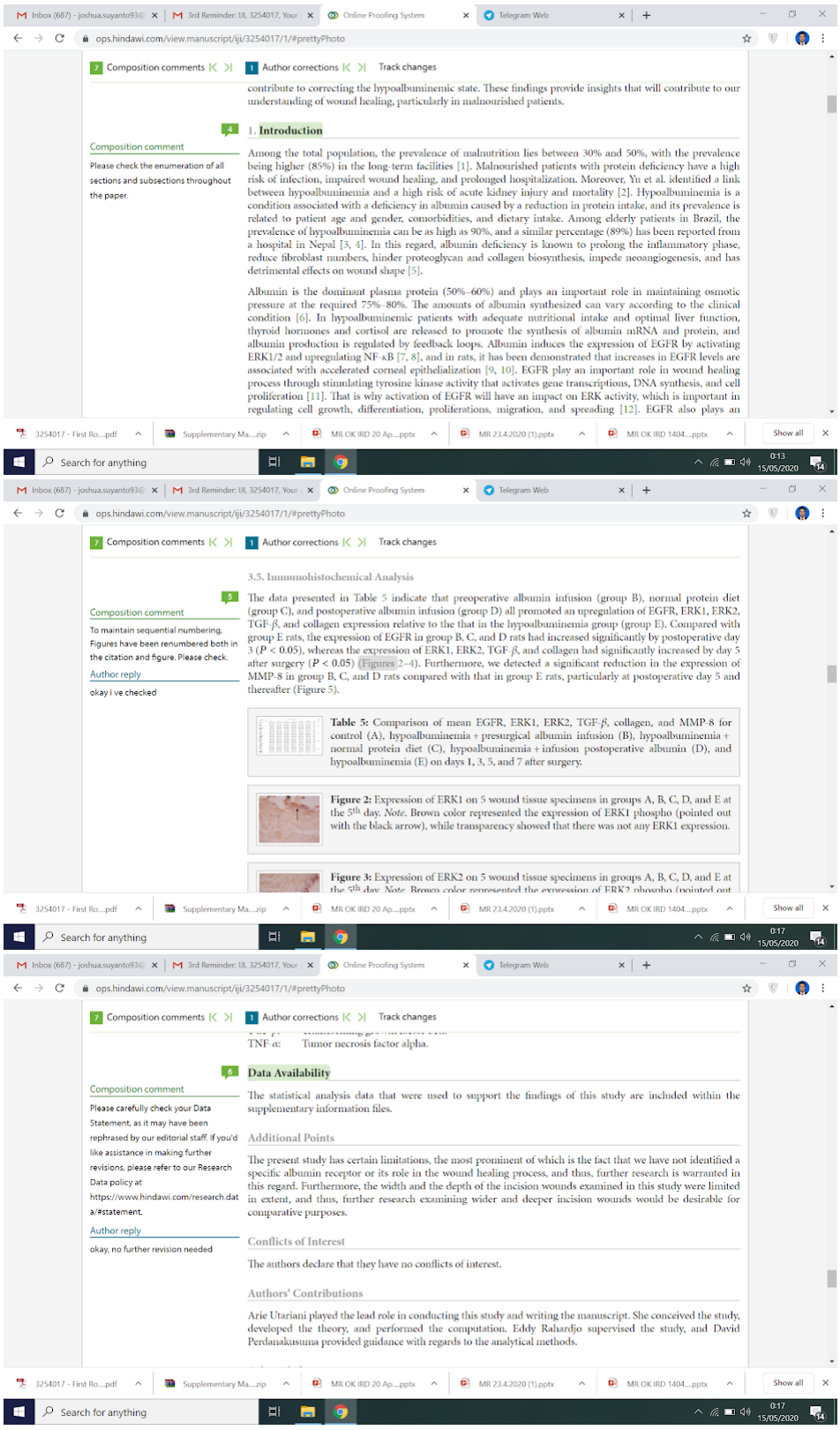

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contribute to correcting the hypoalbuminemic state. These findings provide insights that will contribute to our understanding of wound healing, particularly in malnourished patients.

## 1. Introduction

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Among the total population, the prevalence of malnutrition lies between 30% and 50%, with the prevalence being higher (85%) in the long-term facilities [1]. Malnourished patients with protein deficiency have a high risk of infection, impaired wound healing, and prolonged hospitalization. Moreover, Yu et al. identified a link between hypoalbuminemia and a high risk of acute kidney injury and mortality [2]. Hypoalbuminemia is a condition associated with a deficiency in albumin caused by a reduction in protein intake, and its prevalence is related to patient age and gender, comorbidities, and dietary intake. Among elderly patients in Brazil, the prevalence of hypoalbuminemia can be as high as 90%, and a similar percentage (89%) has been reported from a hospital in Nepal [3, 4]. In this regard, albumin deficiency is known to prolong the inflammatory phase, reduce fibroblast numbers, hinder proteoglycan and collagen biosynthesis, impede neoangiogenesis, and has detrimental effects on wound shape [5].

Albumin is the dominant plasma protein (50%–60%) and plays an important role in maintaining osmotic pressure at the required 75%–80%. The amounts of albumin synthesized can vary according to the clinical condition [6]. In hypoalbuminemic patients with adequate nutritional intake and optimal liver function, thyroid hormones and cortisol are released to promote the synthesis of albumin mRNA and protein, and albumin production is regulated by feedback loops. Albumin induces the expression of EGFR by activating ERK1/2 and upregulating NF-κB [7, 8], and in rats, it has been demonstrated that increases in EGFR levels are associated with accelerated corneal epithelialization [9, 10]. EGFR play an important role in wound healing process through stimulating tyrosine kinase activity that activates gene transcriptions, DNA synthesis, and cell proliferation [11]. That is why activation of EGFR will have an impact on ERK activity, which is important in regulating cell growth, differentiation, proliferations, migration, and spreading [12]. EGFR also plays an

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### 3.5. Immunohistochemical Analysis

5

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Author reply

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The data presented in Table 5 indicate that preoperative albumin infusion (group B), normal protein diet (group C), and postoperative albumin infusion (group D) all promoted an upregulation of EGFR, ERK1, ERK2, TGF-$\beta$, and collagen expression relative to the that in the hypoalbuminemia group (group E). Compared with group E rats, the expression of EGFR in group B, C, and D rats had increased significantly by postoperative day 3 ($P < 0.05$), whereas the expression of ERK1, ERK2, TGF-$\beta$, and collagen had significantly increased by day 5 after surgery ($P < 0.05$) (Figures 2–4). Furthermore, we detected a significant reduction in the expression of MMP-8 in group B, C, and D rats compared with that in group E rats, particularly at postoperative day 5 and thereafter (Figure 5).

**Table 5:** Comparison of mean EGFR, ERK1, ERK2, TGF-$\beta$, collagen, and MMP-8 for control (A), hypoalbuminemia + presurgical albumin infusion (B), hypoalbuminemia + normal protein diet (C), hypoalbuminemia + infusion postoperative albumin (D), and hypoalbuminemia (E) on days 1, 3, 5, and 7 after surgery.

**Figure 2:** Expression of ERK1 on 5 wound tissue specimens in groups A, B, C, D, and E at the 5th day. *Note.* Brown color represented the expression of ERK1 phospho (pointed out with the black arrow), while transparency showed that there was not any ERK1 expression.

**Figure 3:** Expression of ERK2 on 5 wound tissue specimens in groups A, B, C, D, and E at the 5th day. *Note.* Brown color represented the expression of ERK2 phospho (pointed out

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TNF-α: Tumor necrosis factor alpha.

## Data Availability

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Author reply

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The statistical analysis data that were used to support the findings of this study are included within the supplementary information files.

## Additional Points

The present study has certain limitations, the most prominent of which is the fact that we have not identified a specific albumin receptor or its role in the wound healing process, and thus, further research is warranted in this regard. Furthermore, the width and the depth of the incision wounds examined in this study were limited in extent, and thus, further research examining wider and deeper incision wounds would be desirable for comparative purposes.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Authors' Contributions

Arie Utariani played the lead role in conducting this study and writing the manuscript. She conceived the study, developed the theory, and performed the computation. Eddy Rahardjo supervised the study, and David Perdanakusuma provided guidance with regards to the analytical methods.

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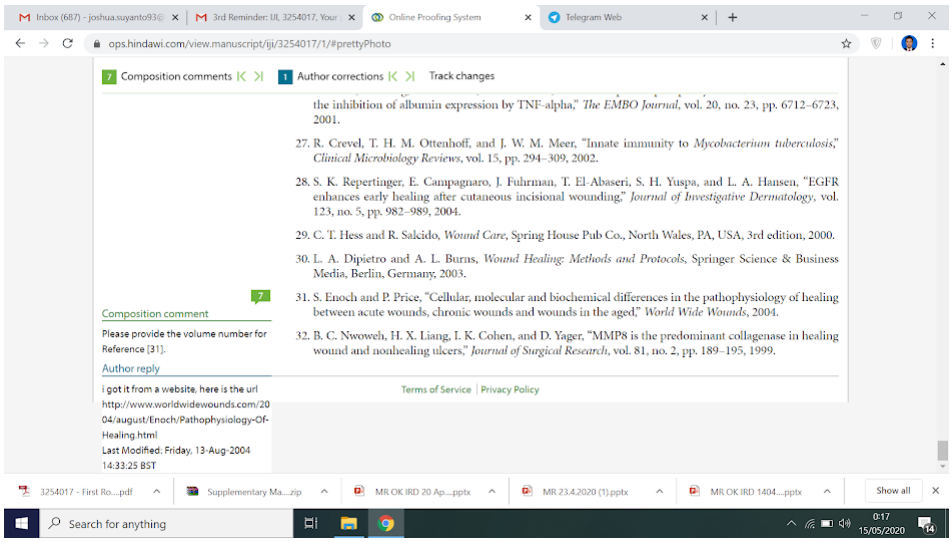


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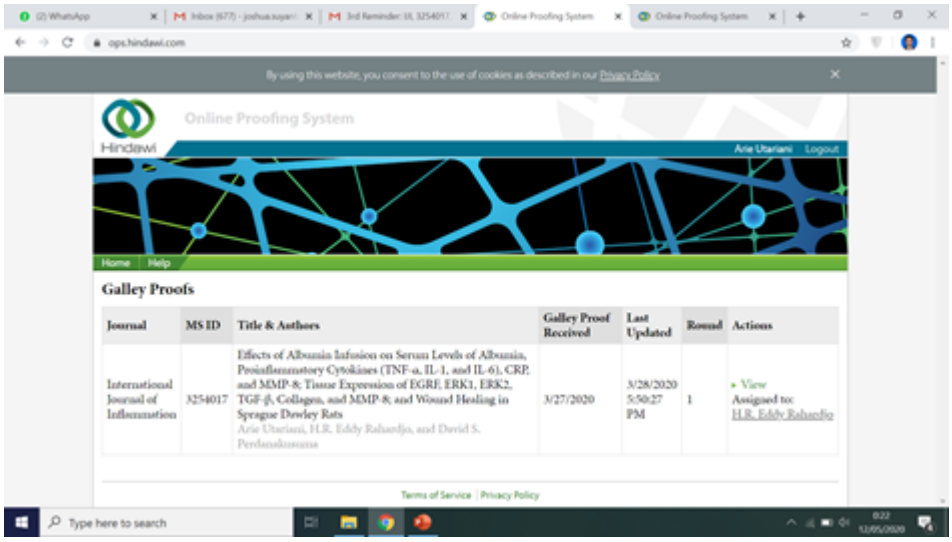


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