

Association between anemia and gastrointestinal malignancy among male patients in a university hospital in Riyadh, Saudi Arabia

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ABSTRACT

Introduction: Iron deficiency was reported as the most common nutritional deficiency in developing and developed countries. Many studies reported that iron deficiency anemia (IDA) is related to the development of gastrointestinal (GI) malignancies **Aim:** The current study aimed at investigating the prevalence of iron deficiency anemia among Saudi patients subjected to endoscopy procedure, and to assess the association between iron deficiency anemia and GI malignancy. **Method:** A retrospective study was performed over 244 Saudi patients attending King Saud University Hospital (KSUH) in Riyadh, Saudi Arabia between 2015 and 2018. Data were collected from the hospital database (esih). Patients aged 30 years or more were recruited in this study. They had to be subjected to endoscopy before the recruitment period. Complete blood count analysis was performed for the blood samples collected from the patients. **Results:** The findings of the study showed that the prevalence of IDA among Saudi patients was 63.5%. Gastritis (15.16%), colon carcinoma (13.11%), and polyps (12.7%) were the most reported endoscopy results among patients with IDA. In addition, it was found that there is no significant association between IDA and GI malignancy. **Conclusion:** The study concluded that despite the reported significant association between IDA and GI malignancy, the current study revealed that there is no significant association between IDA and GI malignancy. This might be attributed to sample-related issues, which require more extended studies investigating larger sample sizes, in addition to including ferritin level measurements for the investigated patients.

Keywords: GI malignancy and male patients, iron deficiency anemia, prevalence

Introduction

Anemia is split into three categories based on the mean cell volume (MCV). MCV is a representation of the average size of red blood cells (RBCs).^[1] Anemia is divided into causes that lead to microcytic anemia, normocytic anemia, and macrocytic anemia.^[2] Microcytic anemia is defined as an MCV less than 80, normocytic from 80 to 100, and macrocytic with an MCV greater than 100.^[3]

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The causes of microcytic anemia include sideroblastic anemia, iron deficiency anemia, thalassemia, and anemia of chronic disease.^[4]

Iron deficiency anemia is when the body does not have enough iron to produce RBCs and the body becomes deficient in iron due to lack of iron in the diet, poor absorption, or bleeding.^[5] Iron enters through our diet and is absorbed in the small intestine, specifically in the duodenum. Dietary iron is in the Fe⁺³ state and is converted to the Fe⁺² state. A transporter called the divalent metal transporter 1 or DMT 1 shuttles the first ion from the duodenum into the cell within the enterocyte which is a cell that lines the duodenum (Talukder, 2021). Ferroportin on the basal side of the enterocyte shuttles the ferrous iron into the bloodstream.

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On the other hand, if your body has enough iron, the ferrous iron is bound to ferritin and it remains within the enterocyte. If the iron bound to the ferritin is not utilized, it will eventually be lost when the enterocyte completes its natural lifecycle and dies.^[6] Hepcidin is the main regulator of iron absorption within the body. Iron is stored in the body within specialized cells in the liver called Cooper cells. When the iron stores are full, hepcidin is released by liver cells called hepatocyte.^[7] Hepcidin binds to the ferroportin transporter, which down regulates its activities. As a result, the iron remains in the enterocytes and is not absorbed into the body. Inflammation can also trigger hepcidin release preventing iron utilization in times of significant inflammation.^[6]

Gastrointestinal abnormalities were reported as a major cause of IDA. Malabsorption of iron is common after some forms of gastrointestinal surgeries (most of the iron taken in by foods is absorbed in the upper small intestine). Any abnormalities in the gastrointestinal tract can alter iron.^[6-8]

Since the gastrointestinal (GI) malignancy was significantly more common in anemic patients based on cohort study, multiple studies were done to see the association between anemia and GI malignancy.^[8]

A cross-sectional study was conducted in Kashmir comparing two groups of patients with IDA and one group without IDA. The results showed a high incidence of GI malignancies in the IDA group where 29% were found to have malignancy.^[9]

Another prospective study was done at the Meir Hospital, Israel, on patients with asymptomatic IDA where endoscopy and abdominal CT with contrast were done. The study showed that 29% were found to have malignancy predominance at right-sided colon carcinoma.^[10]

A retrospective study was done on proven colorectal carcinoma. The results showed that IDA was a common clinical manifestation of patients with colorectal carcinoma (51%).^[11]

Relevance to Practice of Primary Care Physicians

This study is significant to the practice of primary care physicians as it provides a more in-depth overview of the relation between IDA and GI malignancy among the patients in the Saudi context. In addition, this study will spark more extended research trials that investigate the prevalence, effect, and association of anemia of different types to the GI abnormalities and disorders. The results of this study will provide sufficient research-based evidence that might warrant early detection and screening by endoscopy at different age stages among GI patients.

Questions of the Study

The overarching concern of this study is to answer the following questions:

1. What is the prevalence of GI malignancies among Saudi male GI patients with IDA?
2. Is there a significant association between iron deficiency anemia and GI malignancy among adult Saudi patients?

Research Objectives

- To find the prevalence of GI malignancy in male patients with IDA.
- To assess the relation between IDA and GI malignancy in male patients.

Hypotheses

We hypothesize that the GI malignancy increased among male patients with IDA.

Methodology

- **Study design:** Retrospective Study
- **Setting:** Male patients attending KSUH in Riyadh, Saudi Arabia.
- **Time period:** 2015–2018.
- **Inclusion criteria:** All male patients aged 30 or above who did GI endoscopy in the period between 2015 and 2018.
- **Exclusion criteria:** Males of age above 30 with no endoscopy and those who were less than 30.
- **Sample sizes:** The study sample was selected conveniently based on the available number of patients in the selected setting, with a sample size of (282), calculated using G power 3.1.9.2 software second version. Using the power of 0.80, alpha (α) of 0.005, and a medium-size effect of 0.5, with the difference between two dependent means. To overcome the dropout problem 15% and to overcome the effect of being a multicenter study such as technical issues another 15% were added. Furthermore, another 15 were added to be more conservative. This yielded a total number of 301 participants as a sample size of the current study. In the final stage of the study sample recruitment, only 244 patients were included in this study after the removal of the repeated data, as many patients had repeated data entry or had performed both upper and lower endoscopy, and some others had poor preparations for endoscopy, which required the researchers to exclude them from the study sample.

Data Collection

Data were collected from the hospital database (esih). Figure 1 shows the sampling process procedure. Patients who were 30 years old or more were recruited in this study. Patients had to be subjected to endoscopy before the recruitment period. Complete blood count analysis was performed for the blood samples collected from the patients. In addition, ferritin results were recorded. Moreover, taking medications, particularly aspirin and non-steroidal anti-inflammatory drugs (NSAIDs), were recorded in the datasheet.

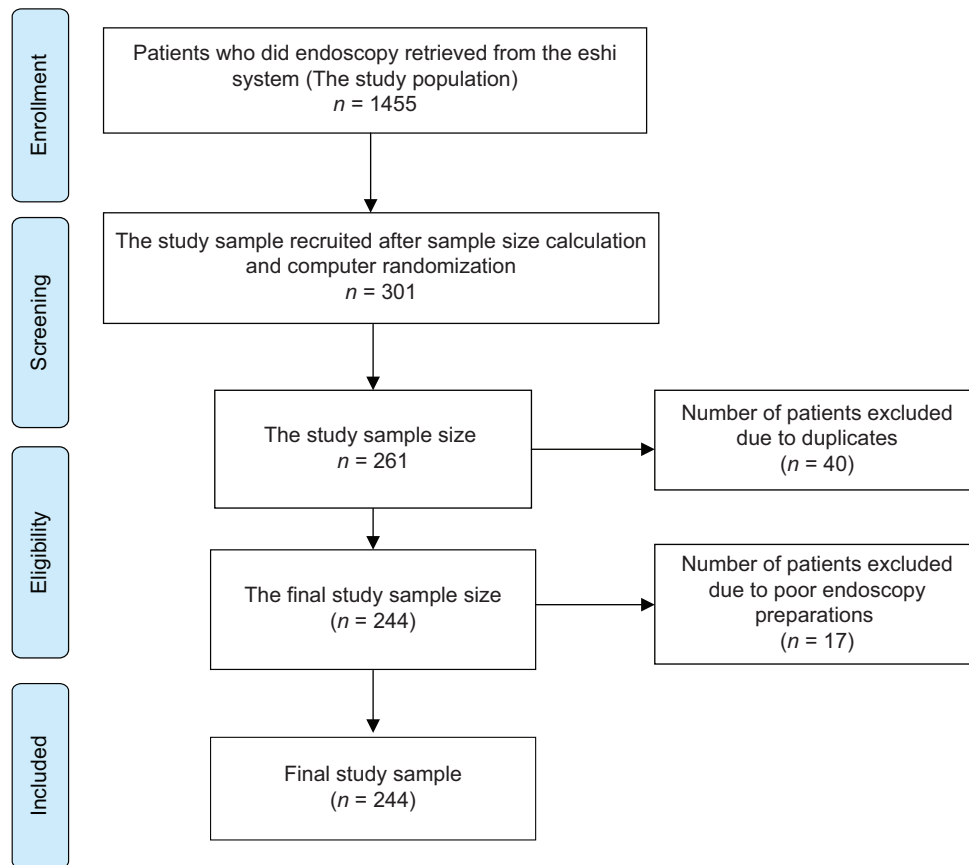


Figure 1: Flow diagram of the patients who did endoscopy and retrieved from the eshi system

The presence of anemia was detected (hemoglobin level of less than 13 g/100 mL). Based on the MCV (less than 80 fL microcytic), and other parameters in the Complete Blood Count (CBC) analysis, the researchers differentiated between iron deficiency and thalassemia. The Mentzer index was used. This index indicated that the product of dividing the MCV over the RBC count in millions revealed the presence of iron deficiency if it is more than 13, otherwise, it revealed the presence of thalassemia if it is less than 13.

Sample technique: convenient sampling.

Data analyses and management

Data was analyzed using the SPSS 26.0 version statistical software. For categorical variables, the Chi-square test was used to test the association. An odds ratio was used to measure the association. A *P* value of ≤ 0.05 and 95% confidence interval were used to report the statistical significance and precision of results. Multivariate logistic regression analysis was utilized to adjust for the confounding factors.

Ethical Considerations

Ethical approval was obtained by the Institutional Review Board (IRB) at KSUH before conducting the study. Patients' information (e.g., names, MRNs) were kept confidential. There is no conflict of interest.

Results and Discussion

Results

The purpose of this study was to investigate the prevalence of gastrointestinal malignancy in Saudi male patients with different kinds of anemia, specifically in IDA. This section describes the demographic characteristics and the major findings of the current study.

Participants' demographic and clinical-related characteristics

Table 1 represents the participants' demographic characteristics. As shown in Table 1, patients aged between 50 and 65 years old constituted the highest category of the participants (47.1%), followed by those aged 65–80 years who constituted 31.6%, and patients in the age range of 30–50 years who constituted 19.7%. The least represented category was of those older than 85 years who constituted 1.6%.

Regarding the red cell distribution width (RDW), 64.3% of the study participants had an RDW level higher than 15%, whereas 35.7% of the study participants had an RDW level between 11 and 15%. Almost half of the study participants (51.2%) were taking aspirin or NSAIDs. Measuring the Hemoglobin (HGB) levels among the study participants indicated that 87.7% of the study participants had HGB levels lower than 13 gm/dL, whereas

11.5% and 0.8% had hemoglobin levels ranging between 13 and 17 gm/dL and more than 17 gm/dL, respectively.

The mean cell volume (MCV) measurements indicated that 64.3% of the study participants had MCV levels lower than 80, 34% had MCV levels between 80 and 100, and 1.6% had MCV levels higher than 100. On the other hand, the mean corpuscular hemoglobin (MCH) measurements indicated that 63.5% of the study participants had MCH levels lower than 27, 31.1% had MCH levels between 27 and

32, and 5.3% had MCH levels higher than 32. Finally, the results showed that 64.3% of the study had no gastrointestinal malignancy, whereas 35.7% had a gastrointestinal malignancy.

Participants' distribution according to the type of anemia and results of endoscopy

Results shown in Table 2 represent the participants' distribution according to the type of anemia. It was present among 90.6% of the study participants. In addition, microcytic anemia represented by both IDA and thalassemia was prevalent among 63.5% and 1.2%, respectively. Macrocytic anemia was detected among 4.9%, whereas normocytic anemia was detected among 20.9% of the study participants.

Results shown in Table 2 indicated that rectal carcinoma was the most recorded result of endoscopy in patients with macrocytic anemia. Polyps resulted in 0.82%, colitis resulted in 0.41%, and esophageal varices resulted in 0.41%.

The results shown in Table 2 represent the results of endoscopy in patients with normocytic anemia. The endoscopy procedure revealed that 6.97% were having sigmoid carcinoma, 2.87% polyps, and 2.87% gastritis. The least represented results showed that 2.05% of the patients had colon carcinoma. In addition, rectal carcinoma and inflammatory bowel disease were present among 1.64 and 1.23% of the normocytic anemia patients, respectively. Finally, diverticulosis and gastric carcinoma were present in 0.41% of the normocytic patients.

The results of the endoscopy in patients with IDA presented in Table 2 showed that 15.16% were having gastritis, 13.11% were having colon carcinoma, and 12.7% were having polyps. Hemorrhoids were present among 4.51% of the IDA patients. Each of esophageal varices and rectal carcinoma was present in 2.05% of the individuals having IDA. Inflammatory bowel disease and gastric carcinoma were least present among 0.82 and 0.41% of the IDA patients, respectively.

Table 1: Participants' Demographic and clinical characteristics (N=244)

Variable	F (%)
Age	
30 – 50 years	48 (19.7)
50 – 65 years	115 (47.1)
65 – 80 years	77 (31.6)
More than 85 years	4 (1.6)
Taking Aspirin or NSAIDS	
Yes	125 (51.2)
No	119 (48.8)
Hemoglobin) gm/dL(levels	
Less than 13	214 (87.7)
13 – 17	28 (11.5)
More than 17	2 (0.8)
MCV (fl) levels	
Less than 80	157 (64.3)
80 – 100	83 (34.0)
More than 100	4 (1.6)
MCH (pg) levels	
Less than 27	155 (63.5)
27 – 32	76 (31.1)
More than 32	13 (5.3)
Red Cell Distribution Width (RDW)%	
11.5 – 14.5	87 (35.7)
More than 14.5	157 (64.3)
Having GI malignancy	
Yes	87 (35.7)
No	157 (64.3)

Table 2: results of endoscopy among patients with different types of anemia (N=244)

	Normal n=23 (9.4%)		Anemia			
	F (%)	F (%)	Microcytic n=158 (64.7%)		Normocytic n=51 (20.9%)	Macrocytic n=12 (4.9%)
			Iron deficiency anemia n=155 (63.5%)	Thalassemia n=3 (1.23%)		
Endoscopy result	F (%)	F (%)	F (%)	F (%)	F (%)	F (%)
Colon Carcinoma	4 (17.4%)	32 (13.11)	0 (0%)	0 (0%)	5 (2.05)	0 (0%)
Sigmoid Carcinoma	3 (13%)	4 (1.6)	1 (0.41%)	1 (0.41%)	17 (6.97)	0 (0%)
Rectal Carcinoma	1 (4.3%)	5 (2.05)	0 (0%)	0 (0%)	4 (1.64)	8 (3.23)
Gastric Carcinoma	1 (4.3%)	1 (0.41)	0 (0%)	0 (0%)	1 (0.41)	0 (0)
Polyps	7 (30.4%)	31 (12.7)	1 (0.41)	1 (0.41)	7 (2.87)	2 (0.82)
Gastritis	1 (4.3%)	37 (15.16)	0 (0%)	0 (0%)	7 (2.87)	0 (0)
Normal	5 (21.7%)	18 (7.38)	1 (0.41)	1 (0.41)	3 (1.23)	0 (0)
Hemorrhoids	0 (0%)	11 (4.51)	0 (0%)	0 (0%)	0 (0%)	0 (0)
Colitis	0 (0%)	3 (1.23)	0 (0%)	0 (0%)	3 (1.23)	1 (0.41)
Esophageal varices	0 (0%)	5 (2.05)	0 (0.05)	0 (0.05)	0 (0%)	1 (0.41)
Inflammatory Bowel Disease	1 (4.3%)	2 (0.82)	0 (0%)	0 (0%)	3 (1.23)	0 (0)
Diverticulosis	0 (0%)	3 (1.23)	0 (0.05)	0 (0.05)	1 (0.41)	0 (0)
Peptic ulcer	0 (0%)	3 (1.23)	0 (0%)	0 (0%)	0 (0%)	0 (0)

Table 3: Association between different types of anemia and having GI malignancy

Type of anemia	Source	Sum of Squares	df	Mean Square	F	Sig.
Iron deficiency anemia	Regression	70.486	2	35.243	0.319	0.727
	Residual	26654.153	241	110.598		
	Total	26724.639	243			
Macrocytic anemia	Regression	281.181	2	140.591	1.281	0.280
	Residual	26443.458	241	109.724		
	Total	26724.639	243			
Normocytic anemia	Regression	128.765	2	64.382	0.583	0.559
	Residual	26595.875	241	110.356		
	Total	26724.639	243			

Table 4: Association between different types of anemia and types GI malignancy

	Colon carcinoma	Sigmoid carcinoma	Rectal carcinoma	Gastric carcinoma
Iron deficiency anemia	0.316	0.409	0.537	0.117
Macrocytic anemia	0.631	0.184	0.019	0.427
normocytic anemia	0.307	0.118	0.581	0.490

* Significant at $\alpha \leq 0.05$ **Table 5: Correlation between Gastritis and Aspirin/NSAIDs**

		Value	Asymptotic Standard Error ^a	Approximate Tb	Approximate Significance
Lambda	Symmetric	0.229	0.050	4.124	0.000
	aspirin or NSAIDs Dependent	0.412	0.077	4.279	0.000
	Gastritis Dependent	0.117	0.052	2.128	0.033
Goodman and Kruskal tau	aspirin or NSAIDs Dependent	0.267	0.045		0.000c
	Gastritis Dependent	0.036	0.009		0.000c

a. Not assuming the null hypothesis. b. Using the asymptotic standard error assuming the null hypothesis. c. Based on Chi-square approximation

The results shown in Table 3 indicated that there is no significant association between IDA and GI malignancy as the P value was 0.727, which is higher than 0.05. In addition, results indicated that there was no significant association between macrocytic anemia and GI malignancy as the P value was 0.280, which is higher than 0.05. Furthermore, there was no significant association between normocytic anemia and GI malignancy as the P value was 0.559, which is higher than 0.05.

To ensure the association between IDA, a correlation between IDA and GI malignancy types was performed. The correlation factors between IDA and colon carcinoma, sigmoid carcinoma, rectal carcinoma, and gastric carcinoma were 0.316, 0.409, 0.537, and 0.117, respectively. But all of them were non-significant at $\alpha \leq 0.05$ level.

To ensure the association between macrocytic anemia, a correlation between macrocytic anemia and GI malignancy types was performed. Results shown in Table 4 indicated that there is no significant association between IDA and the investigated kinds of GI malignancies. The correlation factors between macrocytic anemia and colon carcinoma, sigmoid carcinoma, rectal carcinoma, and gastric carcinoma were 0.631, 0.184, 0.019, and 0.427, respectively. But all of them were non-significant at $\alpha \leq 0.05$ level.

To ensure the association between normocytic anemia and different types of GI malignancy, a correlation between

normocytic anemia and GI malignancy types was performed. Results shown in Table 4 indicated that there is no significant association between normocytic anemia and the investigated types of GI malignancy. The correlation factor between normocytic anemia and colon carcinoma, sigmoid carcinoma, rectal carcinoma, and gastric carcinoma were 0.307, 0.118, 0.581, and 0.490, respectively. But all of them were non-significant at $\alpha \leq 0.05$ level.

Association between gastritis and taking aspirin and NSAIDs

The results shown in Table 5 indicated that there is a significant association between taking aspirin/NSAIDs and having gastritis among anemic patients.

Discussion

Recent research studies have indicated that there is an actual indication that physicians tend to do an endoscopy on male patients having IDA. Physicians need to keep in mind the fact that if adult male patients present with unexplained IDA, this will make them order an endoscopy. Patients might have irritation in the esophagus, stomach, or in the duodenum that may lead also to a little bit of bleeding and IDA.

The current study aimed at investigating the prevalence of IDA among male Saudi patients who went under endoscopy

for gastrointestinal disorders. Nearly two-thirds of those patients suffered from IDA, where gastrointestinal disorders including malignancy had to be ruled out as the cause of such red flag. This might be due to poor absorption of iron due to gastrointestinal disorders or due to a diet deficient in iron besides chronic loss of blood. These findings were in line with the prevalence rate reported by Asobayire *et al.* (2001),^[12] who found that the prevalence rate of IDA was ranging between 41 and 63%. In addition, this result is lower than the reported prevalence rate of IDA among patients with gastrointestinal malignancy by Ho *et al.* (2018),^[13] which was 53%. Most of the cases subjected to endoscopy resulted in colonic polyps. This might be because the majority of the investigated patients are old and the polyps might have developed due to the advanced age and growth of the epithelial layers lining the gastrointestinal tract. Gastritis was the second most observed result of endoscopy among the investigated patients. As evidenced by the results, this condition might be developed due to the intake of either aspirin or NSAIDs. Colon carcinoma was found to be the most prevalent GI malignancy among patients with anemia. This result is in accordance with Niv *et al.* (2005),^[10] who reported a strong association between anemia and colon cancer. Iron deficiency was reported as an important marker for colorectal cancer. On the other hand, sigmoid cancer was the most prevalent GI malignancy among patients with normocytic anemia. This might be referred as well to the reported association of colorectal carcinoma to anemia in general. Surprisingly, the results indicated that there was no significant association between the types of anemia including IDA, macrocytic anemia, and normocytic anemia on one hand, and GI malignancy on the other hand. Despite the reported significant association between these disorders, our findings might be attributed to the low sample size of the participants who had GI malignancies of 11%. This result is inconsistent with the results reported by Xavier *et al.* (2018)^[13] that indicated a strong association between IDA and the development of GI malignancy. Furthermore, it was found that taking aspirin/NSAIDs was significantly correlated to gastritis. This result might be attributed to the reported side effects of these drugs on the upper GI side. As it has been reported that 15–40% of the patients taking NSAIDs experience upper GI symptoms. The study revealed that a near-quarter of the chronic users developed a peptic ulcer. This result was supported by the findings of Torbenson (2019),^[14] who reported that consumption of NSAIDs is significantly associated with development of gastritis.

Conclusion

In conclusion, it might be stated that IDA has either direct or indirect significant association with GI malignancies, such as colon carcinoma, rectal carcinoma, sigmoid carcinoma, and gastric carcinoma. Despite that there was no detected association. Still, there must be more extended studies that have to be performed over a longer period and larger samples of GI patients. Implications of the study in terms of practice—the findings of this study revealed a high prevalence rate of GI malignancy among patients with IDA. However, no

significant association was found in this study. According to the research-based evidence reported previously, GI malignancy still must be considered in the clinical judgment of patients with IDA among adult male patients and failure to investigate the cause of anemia especially among male patients of 50 years or above will delay the diagnosis and might worsen the prognosis. So, it is recommended that healthcare providers and policy makers in the healthcare sector hold awareness campaigns regarding the significance of screening by endoscopy among those patients. In terms of research, the findings of this study point to an urgent need to perform a large-scale study over the Saudi population to investigate the association between different types of anemia and the development of GI malignancy.^[15-19]

Implications of the study

In terms of practice, the findings of this study revealed a high prevalence rate of GI malignancy among male patients with IDA. However, no significant association was found in this study. According to the research-based evidence reported previously, GI malignancy must still be considered in the clinical judgment of patients with IDA.

Limitations of the study

The current study is limited to the sample size represented by Saudi patients. Including a larger sample size might yield more accurate and reliable results. In addition, the repetition of the patients' data narrowed down the sample size from 307 to 244 participants, which significantly might be affecting the validity and the generalizability of the study findings. A major limitation of this study is that the researchers could not rely on the ferritin level measurements to investigate the association of IDA with GI malignancy because a significant number of the studied patients (76.4%) had no reported data regarding the ferritin test.

Key Messages

- There is a high prevalence of IDA among Saudi patients.
- Gastritis, colon carcinoma, and polyps were the most reported endoscopy results among patients with IDA.
- There is no significant association between IDA and GI malignancy.

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Conflicts of interest

There are no conflicts of interest.

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