

Nanotechnology-enabled diagnostics for the correlation between serum APN, Cystatin C and MMP-9 levels in patients with hypertension during pregnancy

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Abstract. Nanotechnology is one of the critical factors involved in enhancing the sensitivity of serum biomarker detection. To explore the relationship between serum APN, Cystatin C and MMP-9 levels in patients with hypertension during pregnancy and the severity and prognosis of the disease. A total of 75 cases of hypertensive disorder complicating pregnancy (HDCP) patients who were admitted to the hospital from February 5, 2023 to May 9, 2024, were selected as the study group, and 70 healthy pregnant women who were in the same gestational week were selected as the control group. The serum APN, MMP-9 and Cys C levels of pregnant women and HDCP patients with different disease severity were compared between the two groups, and the receiver characteristic curve (ROC) was used to analyze its diagnostic value. The serum APN, MMP-9 and Cys C levels of HDCP patients with different prognosis were compared, and the factors affecting the prognosis of patients were analyzed by Logistic regression. Nanoparticles could also enable the sensitive detection and quantification of APN, Cystatin C, and MMP-9 in serum samples, thus increasing the accuracy of the study. The serum MMP-9 and Cys C levels of pregnant women in the study group were significantly increased, and the APN level was significantly decreased ($P < 0.05$). Serum MMP-9 and Cys C levels in patients with pregnancy-induced hypertension, mild preeclampsia, and severe preeclampsia gradually increased ($r = 0.768, 0.766; P < 0.001$), and APN levels gradually decreased ($r = -0.748, P < 0.001$). In the diagnosis of patients with HDCP, the sensitivity, specificity and AUC of APN single diagnosis were 70.00%, 82.67% and 9.848 respectively. The sensitivity, specificity and AUC of MMP-9 single diagnosis were 82.86%, 74.67% and 298.300 respectively. The sensitivity, specificity and AUC of Cys C single diagnosis were 80.00%, 74.67% and 1.301 respectively. There were significant differences in age, BMI, parity, dysthymia, disease severity, APN, MMP-9 and Cys between patients with poor prognosis of HDCP and patients with good prognosis of HDCP ($P < 0.001$). The patient's age, BMI, disease severity, APN, MMP-9 and Cys were all related to HDCP. They were related risk factors of HDCP ($P < 0.05$).

Keywords: APN; biomarker; correlation; cystatin C; diagnosis; hypertensive disorder complicating pregnancy; MMP-9; nanotechnology

1. Introduction

Hypertensive disorder complicating pregnancy (HDCP) refers to one of the common complications of pregnancy accompanied by elevated blood pressure. It is common in clinical pregnancy after 20 weeks of pregnancy (Webster *et al.* 2019, Chen *et al.* 2019, Yang *et al.* 2023, Lu *et al.* 2023, Sun *et al.* 2023). With the change of social environment in recent years, the incidence of HDCP is increasing year by year due to bad living habits and diet structure (Salama *et al.* 2019, Guglielminotti *et al.* 2019, Berghouti *et al.* 2023). Patients with severe HDCP will lead to death due to massive hemorrhage in abdominal cavity, which is an important threat to health of mother and infant (Madsen *et al.* 2018, Hu *et al.* 2023, Li *et al.* 2024, Fan *et al.* 2024). At

present, prevention and treatment of HDCP syndrome means that anticonvulsants are used to inhibit the vascular neuromuscular response of patients with HDCP syndrome, and blood pressure of patients is indirectly reduced by relieving vasospasm (Bernstein *et al.* 2017, Vigil-De Gracia *et al.* 2017, Schachter *et al.* 2019). However, relevant studies showed that its effect is relatively slow, and the therapeutic dose has a great influence on the blood drug concentration of patients, so the ideal clinical therapeutic effect cannot be obtained (Okusanya *et al.* 2016, Rohrbach *et al.* 2015). Therefore, it is very important to prevent and treat HDCP from its mechanism (Kreepala *et al.* 2019, Liu *et al.* 2018, Zhang *et al.* 2017, Wang *et al.* 2018, Mehar and Panda 2023).

Relevant reports showed that the changes of inflammation and immune response of pregnant women during pregnancy are all influencing factors that trigger other complications of hypertension (Shi *et al.* 2017, Zhang *et al.* 2019, Fu *et al.* 2024, Hu and Feng, 2017). Adiponectin (APN) is a plasma hormone protein with the function of antagonizing inflammatory mediators, which is closely related to the development of inflammatory reaction, insulin resistance

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and atherosclerosis. According to related reports, lower APN levels may be involved in the occurrence of pre-eclampsia (Adu-Gyamfi *et al.* 2020, Pandey *et al.* 2023). Correa *et al.* (2018) also found that APN may participate in the occurrence and development of HDCP by affecting trophoblast proliferation, trophoblast differentiation, decidual trophoblast invasion and decidual angiogenesis, and may be used as a diagnostic biomarker and treatment target for HDCP (Shin *et al.* 2016, Li *et al.* 2016). Apart from HDCP, renal damage is also common in pregnant women. In order to ensure the safety of mother and infant, early prevention or diagnosis is especially important for a good prognosis. Cystatin C (Cys C) is γ -microprotein and γ -globulin, which is a common detection index clinically reflecting changes in glomerular filtration rate. In recent years, with the in-depth study of HDCP, relevant reports have shown that APN, matrix metalloproteinase-9 (MMP-9) and other related inflammatory response regulatory factors are all related to abnormal secretion of inflammatory factors during the development and progression of HDCP. At present, studies have confirmed that serum APN levels and placental MMP-9 positive level rate are closely related to the severity of hypertension (Lin *et al.* 2018, Xia *et al.* 2017, Bilouei *et al.* 2018). Some studies have found that APN, MMP-9 and Cys C jointly participate in the development and progression of many diseases (Gong *et al.* 2018, Zamanian *et al.* 2017). At present, the relationship between APN, MMP-9, Cys C and the development of HDCP and whether they can be used as potential serum biomarkers for the diagnosis and evaluation of the disease is still unclear. To this end, this study took 75 patients with HDCP who were admitted to the hospital from February 5, 2016 to May 9, 2017, as the study group, and measured serum APN, Cys C and MMP-9 levels, and compared with the healthy pregnant women with the same gestational age to provide more reference for disease diagnosis and treatment.

2. Materials and methods

2.1 Clinical data

The 75 cases of HDCP patients who were admitted to the hospital from February 5, 2023 to May 9, 2024, were treated as the study group. They were 22-35 years old, with an average age of (27.34±3.23) years, and a gestational age of 32-40 weeks, with an average gestational week (34.12 ± 4.52) weeks, disease severity: 29 cases of pregnancy-induced hypertension, 21 cases of mild preeclampsia, and 25 cases of severe preeclampsia. In addition, 70 healthy pregnant women in the same gestational week were selected as the control group. They were 22-38 years old, with an average age of (28.11 ± 3.34) years, a gestational age of 31-40 weeks, and an average gestational age of (34.30 ± 4.56) weeks. There was no statistically significant difference between the two groups of pregnant women in general information ($P>0.05$). See Table 1. The included subjects and their families all signed informed consent forms in advance. This study was approved by the Maternal & Child Care Service Center of Kaizhou Ethics Committee, and all methods were performed in accordance with the Declaration of Helsinki.

2.2 Inclusion criteria

(1) The study group met the HDCP-related diagnostic criteria and classifications in *Obstetrics and Gynecology* (Le, 2008) (7th edition), (2) All were singletons for the first pregnancy, (3) Those with complete medical records and high compliance.

2.3 Exclusion criteria

(1) Combined with hypertension before pregnancy, (2) Combined with vital organ dysfunction, (3) Combined with cognitive and mental disorders, combined with endocrine, blood, urinary, immune system diseases and infectious diseases, (4) Combined other diseases that may affect the measurement indicators of this study.

2.4 Methods

2.4.1 Main reagents and instruments

APN ELISA Test Kit was purchased from Shanghai Guyan Biotechnology Co., Ltd. MMP-9 ELISA Test Kit was purchased from Qingdao Jieshikang Biotechnology Co., Ltd. Cys C ELISA Test Kit was purchased from Shanghai Guyan Biotechnology Co., Ltd. Centrifuge was purchased from Hunan Pingfan Technology Co., Ltd. Automatic Washer was purchased from Nanjing Detie Experimental Equipment Co., Ltd. Enzyme micro-plate reader was purchased from Shanghai Haozhuang Instrument Co., Ltd.

2.4.2 Determination standard

5 mL of fasting peripheral venous blood was drawn from the subjects in the early morning, centrifuged at 3500r/min for 10 minutes to obtain the supernatant, and stored in a refrigerator at -4°C for later use, serum APN, MMP-9, Cys C levels were measured by enzyme-linked immunosorbent assay, all using the same batch and batch number kits and instruments of the same model.

2.5 Statistical methods

SPSS 17.0 (Beijing Boyi Zhixun Information Technology Co., Ltd.) was used for statistical analysis. The counting data between the two groups were tested by X² test. The measurement data are expressed as ($\bar{x}\pm s$). Independent sample t test was used for comparison of measurement data between the two groups. ROC curve was used to evaluate the diagnostic value of serum and serum APN and MMP-9 for HDCP. Logistic regression model was established with APN and MMP-9 as independent variables. The area under ROC curve of the combined detection was fitted by the probability value in the model. The difference was statistically significant with $P<0.05$.

3. Results

3.1 Comparison of general data of two groups of pregnant women

There was no statistically significant difference between

Table 1 Comparison of general data of two groups of pregnant women

Item	Research group (n=75)	Control group (n=70)	t	p-value
Age(year)	27.34±3.23	28.11±3.34	0.042	0.967
BMI	24.10±3.14	24.01±2.41	0.193	0.848
Gestational age(weeks)	34.12±4.52	34.30±4.56	0.239	0.812

Table 2 Comparison of serum APN, MMP-9 and Cys C levels between two groups of pregnant women

Group	n	APN(μg/mL)	MMP-9(mg/mL)	Cys C(mg/L)
Research group	75	8.23±1.69	317.20±50.03	1.74±0.52
Control group	70	12.21±1.67	280.11±32.00	1.13±0.24
t		1.4252	5.276	8.963
p-value		<0.001	<0.001	<0.001

Table 3 Relationship between serum levels of APN, MMP-9 and Cys C and severity of HDCP

Severity of disease	n	APN(μg/mL)	MMP-9(mg/mL)	Cys C(mg/L)
Pregnancy hypertension	29	8.89±1.13	293.48±18.25	1.42±0.16
Mild preeclampsia	21	8.21±1.12	339.75±15.43	1.69±0.18
Severe preeclampsia	25	7.35±1.14	362.24±17.37	1.81±0.15
F		5.795	8.382	9.271
p-value		<0.001	<0.001	<0.001

Table 4 Diagnostic value of APN, MMP-9 and cystatin C in HDCP

Indexes	APN	MMP-9	Cys C
AUC	0.8385	0.8162	0.8265
Std. Error	0.03349	0.03720	0.03660
95%CI	0.7728 to 0.9041	0.7433 to 0.8891	0.7547 to 0.8982
Cut-off value	9.848	298.300	1.301
Sensitivity (%)	70.00	82.86	80.00
Specificity (%)	82.67	74.67	74.67

the two groups of pregnant women in age, gestational age, and BMI ($P>0.05$), and they were comparable. See Table 1.

3.2 Comparison of serum APN, MMP-9 and Cys C levels between two groups of pregnant women

The serum MMP-9 and Cys C levels of pregnant women in the study group were significantly increased, and the APN level was significantly decreased ($P<0.05$). See Table 2.

3.3 Relationship between serum levels of APN, MMP-9 and Cys C and severity of HDCP

Serum MMP-9 and Cys C levels in patients with pregnancy-induced hypertension, mild preeclampsia, and

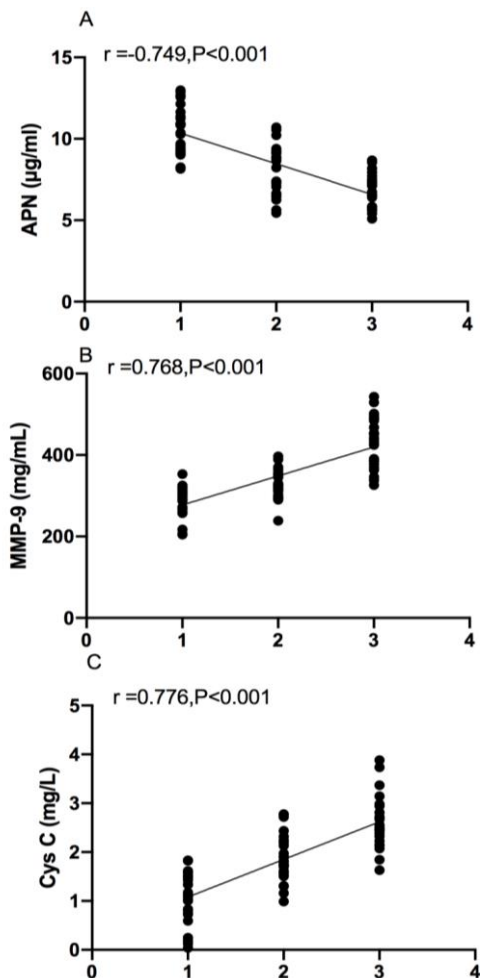


Fig. 1 Relationship between serum levels of APN, MMP-9 and Cys C and severity of HDCP (A. The level of serum APN was negatively correlated with the severity of HDCP ($r=-0.748$, $p < 0.001$). B. The level of serum MMP-9 was positively correlated with the severity of HDCP ($r=0.768$, $P<0.001$). C. The level of serum Cys C was positively correlated with the severity of HDCP ($r=0.766$, $P<0.001$))

severe preeclampsia gradually increased ($r=0.768$, 0.766 , $P<0.001$), and APN levels gradually decreased ($r=-0.748$, $P<0.001$), the difference was statistically significant ($P<0.05$). See Table 3, Fig. 1.

3.4 The diagnostic value of APN, MMP-9, Cys C in HDCP

In the diagnosis of patients with HDCP, the sensitivity, specificity and AUC of APN single diagnosis were 70.00%, 82.67% and 9.848 respectively. The sensitivity, specificity and AUC of MMP-9 single diagnosis were 82.86%, 74.67% and 298.300 respectively. The sensitivity, specificity and AUC of Cys C single diagnosis were 80.00%, 74.67% and 1.301 respectively. See Table 4, Fig. 2.

3.5 Relationship between serum APN, MMP-9, Cys C levels and prognosis of HDCP

There were significant differences in age, BMI, parity,

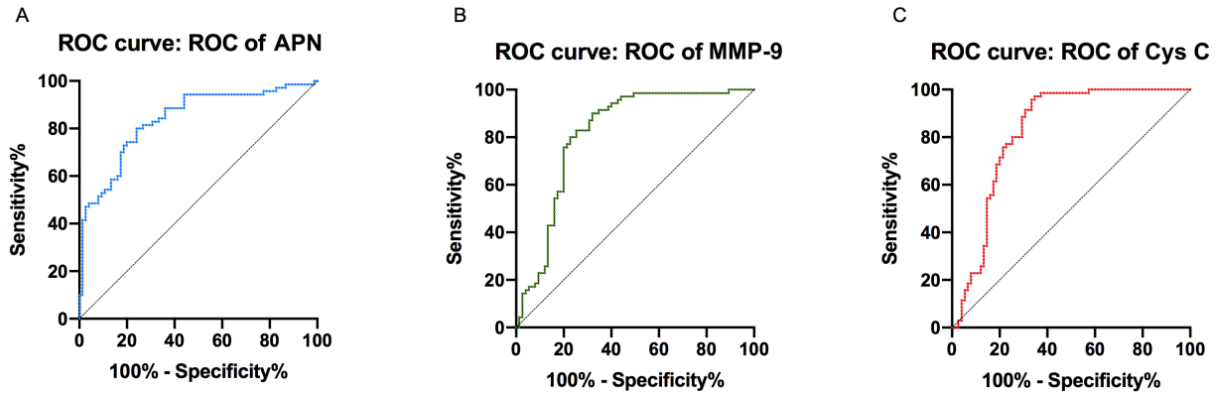


Fig. 2 ROC curve of serum APN, MMP-9, Cys C in diagnosis of HDCP ((A) The sensitivity and specificity of serum APN in diagnosis of HDCP were 70.00% and 82.67%, respectively. (B) The sensitivity and specificity of serum MMP-9 in diagnosis of HDCP were 82.86% and 74.67%, respectively. (C) The sensitivity and specificity of Cys C in diagnosis of HDCP were 80.00% and 74.67%, respectively.)

Table 5 Relationship between serum APN, MMP-9, Cys C levels and prognosis of HDCP

Item	Good prognosis	Poor prognosis	X ² /t	p-value
Age(year)			16.740	<0.001
<25	35 (70.00)	5 (20.00)		
≥25	15 (30.00)	20 (80.00)		
BMI (kg/m ²)			19.050	<0.001
<24.90	44(88.00)	10(40.00)		
≥24.90	6(12.00)	15(60.00)		
APN (μg/mL)	13.2±1.70	7.10±1.70	14.650	<0.001
MMP-9 (mg/mL)	280.11±32.00	317.20±50.03	3.896	<0.001
Cys C (mg/L)	1.10±0.20	1.70±0.50	5.758	<0.001

dysthymia, disease severity, APN, MMP-9 and Cys between patients with poor prognosis of HDCP and patients with good prognosis of HDCP (P<0.001). See Table 5.

3.6 Logistic regression analysis of prognostic factors of HDCP

The patient’s age, BMI, disease severity, APN, MMP-9 and Cys C were all related to HDCP. They were related risk factors of HDCP (P<0.05). See Table 6 and 7.

3.7 The effect of nanotechnology in biomarker detection

The Table 8 below compares the conventional methods of detection with nanotechnology-enhanced detection of serum biomarkers APN, Cystatin C, and MMP-9 related to hypertension severity in pregnancy. Traditional methods have only moderate sensitivity and higher detection limit, that is, they are less capable of detecting lower concentrations of biomarkers. This limitation leads to greater variability in measurements, making it harder to distinguish between different severities of hypertension. This table shows that

Table 6 Assignment table

Related factors	Assignment description
Age(year)	<25=0, ≥25 =1
BMI (kg/m ²)	<24.90=0, >24.90=1
Disease severity	Pregnancy hypertension=0, Mild preeclampsia=1, Severe preeclampsia=2
APN (μg/mL)	<7.10=0, >7.10=1
MMP-9 (mg/mL)	<317.20=0, >317.20=1
Cys (mg/L)	<1.70=0, >1.70=1

Table 7 Logistic regression analysis of prognostic factors of HDCP

Factors	β	SE	Wald	p-value	Exp(β)	95%CI
Constant	0.943	0.503	16.013	0.052	2.504	1.746 ~ 18.000
Age	0.799	0.200	16.182	0.076	1.123	0.800 ~ 10.044
Disease severity	0.780	0.286	15.200	0.003	2.095	1.706 ~ 12.008
APN	0.458	0.193	8.552	0.014	2.016	0.498 ~ 15.001
MMP-9	-0.811	0.179	7.800	0.001	0.169	0.193 ~ 2.180
Cys C	0.759	0.194	18.781	0.002	2.401	0.178 ~ 5.042

those conventional techniques have moderate accuracy to correlate biomarker levels with disease severity, therefore leading to a limited prognostic value and a time-to-detection that is slow. These are relatively high-cost methods with only moderate applicability for early diagnosis.

In comparison, the nanotechnology enhancement of such detection capabilities is immense. In Table, nanotechnology provides very high sensitivity and a low limit of detection, offering an avenue for more accurate and trustworthy measures. There will thus be sharper distinctions between different severity levels of hypertension, which will greatly enhance the accuracy of correlations between the levels of biomarkers and diseases of different severities. It also gives better prognostic value and a faster time to detection, hence being a very powerful tool for early diagnosis. Although it may be expensive in the short run, nanotechnology’s cost-effectiveness in the long run due to

Table 8 The effect of nanotechnology in biomarker detection

Parameter	Traditional detection	Nano-enhanced detection
Sensitivity	Moderate	High
Detection Limit	Higher (less sensitive)	Lower (more sensitive)
Accuracy of Severity Correlation	Moderate	High
Variability in Measurements	High	Low
Prognostic Value	Limited	Enhanced
Distinctness of Biomarker Levels	Less distinct among severity levels	More distinct among severity levels
Time to Detection	Longer	Shorter
Applicability to Early Diagnosis	Limited	Significant
Cost of Detection	Moderate to High	Higher initially, but cost-effective long-term

increased precision and efficiency makes it such an advancement in the medical field, more especially in the management of pregnancy-related hypertension.

4. Conclusions

Serum biomarkers play an increasingly important role in preventing and treating the development and progression of diseases. Previous studies have shown that MMPs are involved in the two stages of vascular remodeling during the placental formation stage of preeclampsia and the development of hypertension caused by vascular basement membrane damage. Studies have shown that MMP-9 plays an important role in the abnormal process of immune system and inflammatory mechanism in patients with HDCP. The differential level of MMP-9 in HDCP was found in some functional studies of MMP-9 (Behrens *et al.* 2016). Diagnosis and treatment of patients with HDCP can reduce the risks of complications and other autoimmune dysfunction. Therefore, it is of great clinical significance to search for biological indicators closely related to the diagnosis and treatment of HDCP (Ren *et al.* 2018).

In this study, we first detected the level difference of APN, MMP-9 and Cys C in the serum of patients with HDCP and normal pregnant women by ELISA. The results showed that the level of Cys C and MMP-9 in patients with HDCP was significantly higher than that in healthy pregnant women, while APN was the opposite. Relevant reports suggested that Cys C level was significantly correlated with the condition of hypertension patients with different degrees. However, studies have confirmed that hypertension was closely related to renal dysfunction, so regular monitoring the level of Cys C content can effectively predict and evaluate the disease progression of patients with HDCP. Changes in APN affect the normal function of vascular endothelial function. The level of APN decreased in the process of vascular endothelial cell injury. Studies have shown that the increase of APN level can lead

to the abnormality of autoantibodies and proinflammatory cytokines, which is related to the abnormal mechanism of cardiovascular diseases and vascular endothelial system morphology and function in HDCP patients. However, MMP-9 is a kind of matrix metalloproteinase, and the increase of its level may lead to vascular endothelial injury. The development and progression of HDCP are all related to the change of MMP-9 content in blood. In a similar study, the level of MMP-9 in HDCP patients decreased with the improvement of the disease. At present, although there is no specific study on the interaction between the severity of HDCP and Cys C, APN and MMP-9, there are experiments related to hypertension to detect the level of Cys C, APN and MMP-9 in hypertensive patients with different degrees. Based on the analysis results, we speculated that the levels of Cys C, APN and MMP-9 were related to the severity of HDCP. Then, we analyzed the correlation of Cys C, APN and MMP-9 in HDCP with different severity. It was found that the level of serum APN decreased and the level of Cys C and MMP-9 increased with the increase of severity. Cys C and APN have been proved to be closely related to the assessment of disease, their levels also show significant increase or decrease with the progression of disease. Logistic univariate and multivariate analysis of risk factors related to prognosis in patients with HDCP showed that severity, APN, mmp-9 and Cys C were independent risk factors for prognosis of patients with HDCP. Routine and other related examinations such as blood and urine routine are auxiliary examinations for routine clinical examinations in the diagnosis of HDCP. There is a certain degree of misdiagnosis and missed diagnosis rate for the specific disease severity of HDCP in vivo. The combination of a marker can better improve the diagnostic efficiency. Finally, we analyzed the diagnostic value of Cys C, APN, MMP-9 in HDCP. By drawing ROC curves, we found that Cys C, APN and MMP-9 single diagnosis had good sensitivity and specificity in the diagnosis of patients with HDCP. The results show that the determination of serum APN, MMP-9 and Cys C levels has clinical application value for the diagnosis and prognosis of HDCP patients.

In summary, serum MMP-9 and Cys C levels in HDCP patients are significantly increased, and APN levels are significantly reduced. The three may be involved in the occurrence and development of HDCP, and may become potential serum biomarkers for disease diagnosis and prognosis evaluation. This study confirmed the level and predictive value of APN, MMP-9 and Cys C in patients with HDCP, but there are still some deficiencies in the study. For example, there is no more specific analysis of the regulatory effect of APN and MMP-9 level changes on HDCP, and no further explanation of their biological functions. In addition, APN, MMP-9 and clinical markers of HDCP were not analyzed, which had certain influence on the improvement of study design. Therefore, we will refer to the latest research in real time in the later period and add corresponding research schemes to make up for design defects, so as to continuously improve the research. Also, nanotechnology provides very high sensitivity and a low limit of detection, offering an avenue for more accurate and trustworthy measures.

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