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Effect of glomerulosclerosis index, tubular index, and matrix metalloprotein against serum creatinine and estimated glomerular filtration rate in obstructive kidney stone patients in Sanglah General Hospital Denpasar Bali

Oka, A. A. G.,¹ Sun Fu²

ABSTRACT

Objective: Kidney stones is one of the many causes of chronic kidney disease (CKD) in clinical and kidney fibrosis in histopathology presentation. Its occurs characterized by the presence of glomerulosclerosis (GS), tubulointerstitial fibrosis (TIF) and tubular atrophy (TA). This research aims to find out that the effect of glomerulosclerosis index (GSI), tubular index (TI), and matrix metalloprotein (MMP-9) against serum creatinine (SC) and estimated glomerular filtration rate (eGFR) in kidney stone disease.

Method: A total of 62 samples of kidney biopsy patients during kidney stone surgery in Sanglah General Hospital Denpasar-Bali, from February until December 2013. Kidney tissue biopsy stained with Masson's Trichrome. Determination of GSI was counted GS in 30 glomerular in power field 400, and TI was counted normal tubular in 30 glomerular in power field 400, and MMP-9 was carried out using Kit Methode. Structural Equation Modelling (SEM) program Analysis of Moment Structure (AMOS) was used to analyze the effect of GSI, TI, and MMP-9 against SC and eGFR in kidney stone patients.

Results: Descriptive analysis were male 43 (69.35%), and female 19 (30.65%). Age (years) 50.0 ± 10.56 ; SC (mg/dl) 1.71 (0.47 to 6.76); GSI (glomerulosclerosis/30 glomerular) 11 (0-30); TI (normal tubulars/30 glomerular) 850.24 (118 to 1523); eGFR (ml/min) 65.41 ± 20.47 ; Leukocytes (cells/mm³) 7.82 ± 1.89 ; and MMP-9 (ng/ml) 6.13 (0.05 to 28.37). Direct and total effect (direct and indirect effect) were GS to eGFR = -0.16 and 0.33; TI to eLFG = 0.28 and 0.36, GS to SC = 0.31; TI to SC = -0.14; MMP-9 to SC = -0.16; SC to eGFR = -0.55.

Conclusion: Direct and total effect of GSI to eGFR were negative (-) 16% and (-) 33%; TI to eGFR were positive (+) 28% and (+) 36%. Direct effect (without indirect effect; direct effect as same as a total effect) of GSI, MMP-9, and TI to SC were positive (+) 31%, negative (-) 16%; and negative (-) 14% consecutively. Direct effect or total effect of SC to eGFR were negative (-) 55%. The results concluded that the effect measurements of urinary MMP-9, and GSI, and TI score to SC were negative (-) 16%, positive (+) 31% and negative (-) 14% consecutively. The effect measurements of urinary MMP-9, and GSI, and TI score to eGFR were negative (-) 0.09%, negative (-) 16%, and positive (+) 28%.

Keywords: kidney stone; estimated glomerular filtration rate; glomerulosclerosis index; tubular index; matrix metalloprotein.

Cite This Article: Oka, A. A. G., Sun Fu. 2018. Effect of glomerulosclerosis index, tubular index, and matrix metalloprotein against serum creatinine and estimated glomerular filtration rate in obstructive kidney stone patients in Sanglah General Hospital Denpasar Bali. *Bali Medical Journal* 7(2): 379-384. DOI:10.15562/bmj.v7i2.1054

^{1&2}Department of Surgery, Faculty of Medicine, Udayana University/ Sanglah General Hospital, Denpasar-Bali

INTRODUCTION

The kidney has a complex structure. It is divided into functional units, called nephrons, comprised of the filtering apparatus, the glomerulus, and an apparatus that regulates fluid and electrolyte homeostasis, the tubule, that have both a filtering and a reabsorbing component. Mechanical renal stone obstruction causes back up of intraparenchymal urine flow and increased intraluminal nephrons pressure. That initial episode obstruction can increase the renal blood flow and decrease renal blood flow and increase renal lymphatic flow for the next episode. A chronic episode of obstructive kidney stone disease causes tubular atrophy and glomerulosclerosis or renal parenchymal fibrosis and decrease of kidney functions.

GFR cannot be measured directly. Estimated glomerular filtration rate (eGFR) is a common laboratory examination to estimate the kidney function. The best estimate of GFR can be obtained by measuring the rate of clearance of a given substance from the plasma. The substance must be able to achieve a stable plasma concentration, be freely filtered across the glomerulus, not be secreted, reabsorbed, synthesized, or otherwise metabolized by the renal tubules, and not be impacted by any other means of removal from the plasma. There are some substances that have been used clinically to estimate GFR, including inulin, radiolabelled compounds, and creatinine. Creatinine is the most widely used estimate of GFR. Endogenous

*Correspondence to: A. A. G. Oka, Department of Surgery, Faculty of Medicine, Udayana University/ Sanglah General Hospital, Denpasar Bali-Indonesia
okaaag@yahoo.com

Received: 2017-12-01
Accepted: 2018-2-2
Published: 2018-5-1

creatinine, which is produced at a constant rate, but the rate of production varies from individual to individual. Creatinine also cleared from the plasma through proximal tubular secretion, which causes a creatinine clearance (CrCl) overestimates true GFR. It becomes even more important as GFR declines, and tubular secretion increases in response to increasing serum creatinine levels, that considered the upper limit of the true GFR.¹

Plasma Marker, including Plasma creatinine (PCr), Plasma urea, and Plasma cystatin C, can be used as surrogate markers of GFR. PCr is the most widely used plasma marker of GFR. The absolute rate depends on muscle mass, which in turn is influenced by age, sex, and body mass. The relationship of PCr to GFR is relatively constant, and the PCr changes can be used to predict GFR changes. Every 50% GFR decrease resulting in a doubling increase of PCr. The limitations of PCr use, including As GFR falls, creatinine tubular secretion increases; so, PCr may not change noticeably until there has been a significant GFR decrease.¹ PCr production may increase in states of increased muscle breakdown (e.g., rhabdomyolysis, increased dietary protein intake or supplementation), leading to an underestimation of true GFR. Creatinine production may decrease with liver cirrhosis, leading to an overestimation of true GFR.¹

The Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) formulas are mathematical formulas that have been developed to improve the accuracy of the PCr estimation of GFR, and the most widely used.² Cockcroft-Gault is originally developed from data collected from individuals with normal renal function; it is a simple formula to estimate CrCl (not GFR) that corrects for age, sex, and body mass.³ It has the advantage of being very simple but is not as accurate as other methods when renal function is impaired.

MDRD formulas is a series of formulas derived from data collected in patients with severe renal impairment; they are more complex and more accurate than the Cockcroft-Gault. The simplest estimate of GFR is the four-variable equation (PCr, age, sex, and ethnicity).³

The common pathogenesis of progressive chronic kidney disease (CKD) is normal kidney parenchymal (Glomerular and tubular) destruction

$$\text{CrCl} = \frac{(140 - \text{age}) \times (\text{IBW in kg})}{\text{PCr (mg / dL)} \times 72} \times 0.82 \text{ (women)}$$

Figure 1 The Cockcroft-Gault formula³

due to scarring (fibrosis). Four cellular responses are the fundamental pathways that lead to renal fibrosis: (1) An interstitial inflammatory response, (2) a unique interstitial cell population of myofibroblasts appearance, (3) Tubular epithelial cells, (4) interstitial capillary integrity Loss.⁵ The pathogenesis of end-stage renal disease (ESRD) following is renal failure distinguished: (1) Background of decompensated primary and secondary nephrosclerosis, and stenosis of the renal artery. (2) Loss of glomeruli. (3) Disease of the tubules themselves. (4) Renal failure is occurring in primary diseases of the renal cortical interstitium. The renal fibrosis diseases arising from acute interstitial nephritis are dealt with, as also are reflux nephropathy, incomplete obstructive nephropathy, analgesic nephropathy, and chronic interstitial rejection reactions in transplanted kidneys.⁶

The pathologic paradigm for renal progression is advancing tubulointerstitial fibrosis. Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases that substrate specificities controlled by tissue inhibitors of metalloproteinases (TIMPs). The overlapping activity and specificity of MMPs make it difficult to dissect individual actions in vivo. Most studies MMP-2 and MMP-9 in the kidney are degraded collagen type IV, perhaps collagen types I and III, but fail as anti-fibrotic effect.⁷

Kidney fibrosis, which occurs in glomerulosclerosis, interstitial fibrosis, and tubular atrophy, is caused by kidney stones. It is one of the varieties of primary insults of chronic kidney disease (CKD). Imbalance of extracellular matrix (ECM) production and defective ECM degradation by proteolytic enzymes (MMPs), result ECM components accumulate during renal fibrosis. Increased Expression of Intranuclear Matrix Metalloproteinase 9 in Atrophic Renal Tubules Is Associated with Renal Fibrosis.⁸

MATERIALS AND METHODS

The retrospective study, during February to December 2013 were collected 62 microscopic kidneys pathological result of obstructive kidney stone patients, at Pathology Anatomy Department, Sanglah General Hospital in Denpasar Bali. Section of specimens was stain by Masson's Trichrome and examined under light microscope magnification x 200. The glomerulosclerosis index (GSI) was defined by counted of glomerulosclerosis in microscopic fields until a total of 30 glomeruli had been counted, and the tubular index (TI) was defined by

$$\text{GFR (mL/min/1.73 m}^2\text{)} = 186 \times (\text{PCr [mg/dL]})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$$

Figure 2 The Modification of Diet in Renal Disease (MDRD) formulas⁴

counted of normal tubular in microscopic fields until 30 glomeruli had been counted. Examination of the MMP-9 is used by MMP-9 kit (Quantikine Eliza Human MMP-9 Immunoassay). eGFR calculated by CKD-EPI in an accredited Prodia Laboratory. Patient's characteristics expressed using descriptive statistics. Structural Equation Modeling (SEM) program Analysis of Moment Structure (AMOS) was used to analyze the effect of GSI, TI, and MMP-9 against SC and eGFR in obstructive kidney stone patients.

RESULTS

Characteristic Patients

Characteristic of 62 microscopic kidney pathological result of obstructive kidney stone patients were consisted of male 43 (69.35%), and female 19 (30.65%). Age (years) 50.0 ± 10.56 ; SC (mg/dl) 1.71 (0.47 to 6.76); GSI (glomerulosclerosis/30 glomerulars) 11 (0-30); TI (normal tubulars/30 glomerulars) 850.24 (118 to 1523); eLFG (ml/min) 65.41 ± 20.47 ; Leukocytes (cells/mm³) 7.82 ± 1.89 ; and MMP-9 (ng/ml) 6.13 (0.05 to 28.37) (Table 1).

Data Analysis

Data were analyzed using SEM (Structural Equation Modeling) program Analysis of Moment Structure (AMOS) version 21 and test the suitability of the model (Goodness of Fit) in a structural equation. The model is recursive with sample size = 62. The variables of the model are two observed endogenous variables (SC, and eGFR), three observed exogenous variables (GSI, MMP-9, and TI), and two unobserved exogenous variables (E-1, and E-2) as can be seen in Figure 3.

Goodness of Fit Model

Chi-Square (X²), CMIN / DF, Probability level, Root Mean Square Error of Approximation (RMSE), Tucker-Lewis Index (TLI), Comparative Fit Index (CFI), expected Cross Validation Index (ECVI) and Modified ECVI (MECVI) are the criteria fit indices (Table 2). The Chi-Square value 2.400 (DF = 5; P = 0.791). The model is said to be fit if it has a value of Chi-Square P > 0.05 (no significant). The value CMIN / DF acceptable is ≤ 2 and if the value of <1 it can be concluded that the model is very fit. The RMSE value was ≤ 0.05 , that indicate an excellent fit model. TLI and CFI values recommended for indication fit is ≥ 0.95 . If ECVI and MECVI default models < value ECVI and MECVI saturated and independence models, it can be concluded that the model was fit.

Correlations between two construct variables in obstructive kidney stone patients

The correlations between SC and eGFR was negative 0.554 (P = 0.001; CR = -6,862); TI and eGFR was positive 0.280 (P = 0.042; CR = 2.030), there were significant correlations. There were no significant correlations between GSI, TI, and MMP-9 against SC, also GSI against eGFR (Table 3). The coefficient value of determination SC and eGFR showed by Squared Multiple Correlations was 0.181. Which means that the influence of the variables GSI, MMP-9 and TI to SC was 18.1%, and the remaining 81.9% was influenced by other variables outside of the model. The other result of Squared Multiple Correlations was 0.665, it means the influence of the variables GSI, TI and SC to eGFR was 66.5%, and the remaining 33.5% was influenced by other variables outside of the model (Table 3).

The correlations between GSI and TI was negative 0.842 (P = 0.001; CR = -5.030), there were significant correlations. The correlations GSI and TI to MMP-9 was positive 0.241 (P = 0.067; CR = 1.829) and negative 0.195 (P = 0.135; CR = -1.495), there were not significant correlations (Table 4).

Table 1 Characteristics of the study subjects (N =62)

Variables	N (%)	Mean+ SD	Median (Min-Max)
Gender			
Males	43 (69.35 %)		
Females	19 (30.65 %)		
Age (years)		50.0 ± 10.56	
SC (mg/dL)			1.71 (0.47-6.76)
GSI			11 (0-30)
TI			850.24 (118-1523)
eGFR (mL/minutes)		65.41±20.47	
Leucocyte (cells/mm ³)		7.82±1.89	
MMP-9 (ng/mL)			6,13 (0.05-28.37)

GSI=Glomerulosclerosis Index; TI-Tubular Index; SC=Serum Creatinine; eGFR=estimated Glomerular Filtration Rate); MMP-9=Matrix Metalloprotein

Table 2 Goodness of Fit Model Criteria

Criteria	Critical Value	Result Analysis model	Model Evaluation
Chi-Square	expected to small	0.097	Model Fit
CMIN/DF	≤ 2.00	0.097	Model Fit
Probability	≥ 0.05	0.756	Model Fit
RMSE	≤ 0.05	0.000	Model Fit
TLI	≥ 0.95	1.061	Model Fit
CFI	≥ 0.95	1.000	Model Fit
ECVI	Default Model < Saturated	0.0.625 < 0.656 and 2.917	Model Fit
MECVI	and Independence Model	0.692 < 0.727 and 2.952	Model Fit

Table 3 The correlations between two construct variables in obstructive kidney stone patients

			Regression Weights				Standardized Regression Weights
			Estimate	S.E.	C.R.	P	
SC	<---	GSI	0.044	0.030	1.439	0.150	0.312
SC	<---	TI	-0.001	0.001	-0.635	0.525	-0.136
SC	<---	MMP-9	-0.035	0.026	-1.364	0.173	-0.163
eGFR	<---	SC	-13.151	1.917	-6.862	0.001	-0.554
eGFR	<---	GSI	-0.520	0.462	-1.127	0.260	-0.157
eGFR	<---	TI	0.025	0.012	2.030	0.042	0.280

Squared Multiple Correlations, Estimate: SC = 0.181; eGFR = 0.665

Table 4 The correlations between two construct variables in obstructive kidney stone patients

			Covariance's				Correlation Estimate
			Estimate	S.E.	C.R.	P	
GSI	<-->	TI	-2591.893	515.238	-5.030	0.001	-0.842
GSI	<-->	MMP-9	12.963	7.087	1.829	0.067	0.241
TI	<-->	MMP-9	-389.582	260.583	-1.495	0.135	-0.195

Table 5 Effects of variables: GSI, TI, and MMP-9, against SC variable and effects between variables: GSI, TI, and, SC against eGFR variable

	MMP-9à SC	Tlà SC	GSIà SC	MMP-9à eGFR	Tlà eGFR	GSIà eGFR	SCà eGFR
Direct Effects	-0.163	-0.136	0.312	0.000	0.280	-0.157	-0.554
Indirect Effects	-0.000	-0.000	0.000	-0.090	0.076	-0.173	0.000
Total Effects	-0.163	-0.136	0.312	-0.090	0.356	-0.330	-0.554

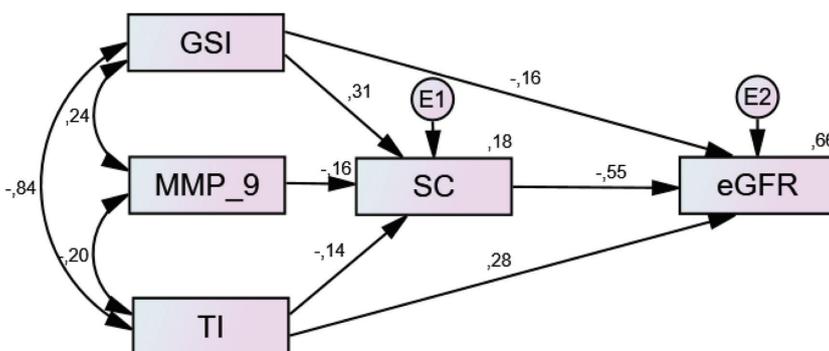


Figure 3 Path Analysis Result of Structural Equation Modeling (SEM) shows the effect between the variables of GSI, MMP-9, TI, SC, and eGFR

Effects between exogenous variables and endogenous variable

The effects between exogenous variables (GSI, TI, MMP-9, and SC) and endogenous variable (eGFR). The effects between variables: GSI, TI, and MMP-9, against SC variable were direct effects, and total effects of GSI to serum creatinine (SC) were most powerful. The direct effects between variables: TI, GSI, and, SC against eGFR variable were 0.28; -0.157; -0.554 (Figure 3, Table 5). The total effects of serum creatinine (SC) to estimated glomerular

filtration rate (eGFR) were most powerful, as seen in Table 5.

DISCUSSION

Effects between variables: GSI, TI, and MMP-9, against SC variable and effects between variables: GSI, TI, and, SC against eGFR variable. Despite the fact that histological lesions were variable in the studied biopsies, the use of the proposed scoring system made it possible to find statistically significant correlations of the renal function at the moment of the biopsy with interstitial lesions (both active and chronic), as well as with glomerulosclerosis and tubular atrophy. The use of a scoring system in glomerulonephritis could permit a unified approach of renal biopsies by different pathologists or nephrologists and could facilitate the study of the histological features involved in the progression of renal disease. Obstructive nephropathy and chronic kidney disease (CKD), characterized by the presence of glomerulosclerosis (GS), tubulointerstitial fibrosis (TIF) and tubular atrophy (TA). Oka et al. (2014) reported a case-control study of 82 samples of kidney biopsy patients during kidney

stone surgery (41 samples with fibrosis as case and 41 samples non-fibrosis as control). The high activity level of caspase-3 was 3.5-fold, and high levels of TGF- β was a 2-fold to gain kidney fibrosis ($P < 0.05$), but high levels of TNF- α was not as a risk factor to gain kidney fibrosis.⁹

Bob et al. reported that there is a correlation between glomerular segmental sclerosis score and serum creatinine. There was a moderate correlation between the renal function with tubulointerstitial scores for chronicity (interstitial fibrosis, tubular atrophy, hyalinosis/fibrosis of interstitial vessels) and also interstitial fibrosis with serum creatinine.¹⁰ We reported that TI has a negative (-0.136) total effect toward creatinine serum and positive (0.355) towards eGFR. Total effect of GSI and creatinine serum and eGFR were 0.312 and -0.330. Total effect creatinine serum towards eGFR-0.554. It means that all this result is comparable to other previous research.

Zhu et al. reported that interstitial fibrosis and tubular atrophy (IFTA) scores in new pathological classification in patients with Diabetic Nephropathy, indicating that IFTA had a strong impact on the renal prognosis. eGFR might be a predictor of the IFTA. Thus, this classification leads to better communication between renal pathologists and clinicians, which provides a logical structure to improve clinical management and efficiency.¹¹

Chang et al., (2006) have revealed a correlation between MMP-2, -9 and serum creatinine concentration, as well as between both MMP-2 and MMP-9 and the severity of CKD. Such correlations may have significant benefits in clinical interpretation.¹² Total effect of MMP-9 and creatinine serum was -0.163. Other previous research contradicted this result. Our research used frozen blood serum in 3 years. It probably there was a protein breakdown during 3 years. It still needed further investigated. The total effect of MMP-9 to SC, and eGFR were negatively 0.163 (-16.3%), and positively 0.090 (9%); Total effect of tubular index (TI) to SC, and eGFR were negatively 0.136 (-13.6%), and positively 0.355 (35.5%); Total effect of glomerulosclerosis index (GSI) SC, and eGFR were positively 0.312 (31.2%), and negatively 0.330 (-33.0%), and total effect of SC to eGFR was negatively 0.554 (-55.4%). Kidney fibrosis, which occurs in glomerulosclerosis, interstitial fibrosis, and tubular atrophy, is caused by kidney stones. It is one of the varieties of primary insults of chronic kidney disease (CKD). Imbalance of extracellular matrix (ECM) production and defective ECM degradation by proteolytic enzymes (MMPs), result ECM components accumulate during renal fibrosis. Tashiro et al. (2004) reported in 47 diabetic nephropathy patients and 14 healthy adults to determine correlations levels of urinary

MMP-9 and type-IV collagen. Patients with diabetic nephropathy were divided into microalbuminuria ($n=27$) and macroalbuminuria ($n=20$). The mean level of urinary MMP-9 and type-IV collagen in diabetic nephropathy patients was significantly higher than those in healthy adults ($P < 0.05$), and the increased levels of urinary MMP-9 and type-IV collagen in accordance with the clinical stage of albuminuria.¹³ Jen-Pi Tsai, et al. (2012) reported that patients high interstitial fibrosis scores (IFS) and high glomerular fibrosis scores (GFS) had higher SC, lower eGFR, and were more likely to have CKD. Univariate analysis showed that IFS and GFS were negatively associated with normal tubular cytoplasmic (NTc) MMP-9 expression and atrophic tubular cytoplasmic (ATc) MMP-9 expression and IFS was positively correlated with atrophic tubular nuclear (ATn) MMP-9 expression. Multivariate stepwise regression indicated that MMP-9 expression in ATn ($r = 0.4$, $p = 0.002$) was an independent predictor of IFS and that MMP-9 expression in the normal tubular cytoplasm ($r = 20.465$, $p = 0.001$) was an independent predictor of GFS. Interstitial fibrosis correlated with MMP-9 expression in the atrophic tubular nuclei.¹⁴ Oka et al. (2015) reported a cross-sectional study in 63 patients with a kidney stone. The results were significant correlation between eGFR and GS index dan TA index ($r = -0.577$; $p = 0.001$ and 0.514 ; $p = 0.001$, consecutively). Multivariate regression equations were $eLFG = 67,21 - 1.63$ (GS index) and $eLFG = 67,21 + 0,01$ (TA index).¹⁵ Bob et al. (2011) reported a retrospective study of 41 renal biopsies patients with primary and secondary glomerulonephritis. Correlation between interstitial fibrosis with SC and GFR were ($R=0.49$, $P=0.0006$) and ($R = -0.59$, $P < 0.0001$); tubular atrophies with SC and GFR ($R=0.41$, $P=0.003$) and ($R = -0.59$, $P < 0.0001$); glomerular segmental sclerosis score with SC and were GFR ($R = 0.3$, $P=0.02$) and ($R = -0.42$, $P=0.003$).¹⁰

CONCLUSION

The coefficient value of determination SC and eGFR showed by Squared Multiple Correlations. The result of Squared Multiple Correlations was 0.181 and 0.665. 0.181 of Squared Multiple Correlations means that the influence of the GSI, MMP-9, and TI to SC was 18.1% and the remaining 81.9% was influenced by other variables outside of the model. The other 0.665. 0.181 of Squared Multiple Correlations means that the influence of GSI, TI, and SC to eGFR was 66.5%, and the remaining 33.5% was influenced by other variables outside of the model. The correlation between MMP-9 to GSI and TI were positive (+) 24 %, and negative (-) 20 % consecutively, and GSI to TI was negative (-) 84 %.

Direct and total effect of GSI to eGFR negative (-) 16% and (-) 33%; TI to eGFR were positive (+) 28% and (+) 36%. Direct effect (without indirect effect; direct effect as same as a total effect) of GSI, MMP-9, and TI to SC were positive (+) 31%, negative (-) 16%; and negative (-) 14%. Direct effect or total effect of SC to eGFR were negative (-) 55%. The results concluded that the effect measurements of urinary MMP-9, and GSI, and TI score to SC were negative (-) 16 %, positive (+) 31 % and negative (-) 14 % consecutively. The effect measurements of urinary MMP-9, and GSI, and TI score to eGFR were negative (-) 0.09 %, negative (-) 16 %, and positive (+) 28 % consecutively.

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