FIG. 1

Numere totale de celule

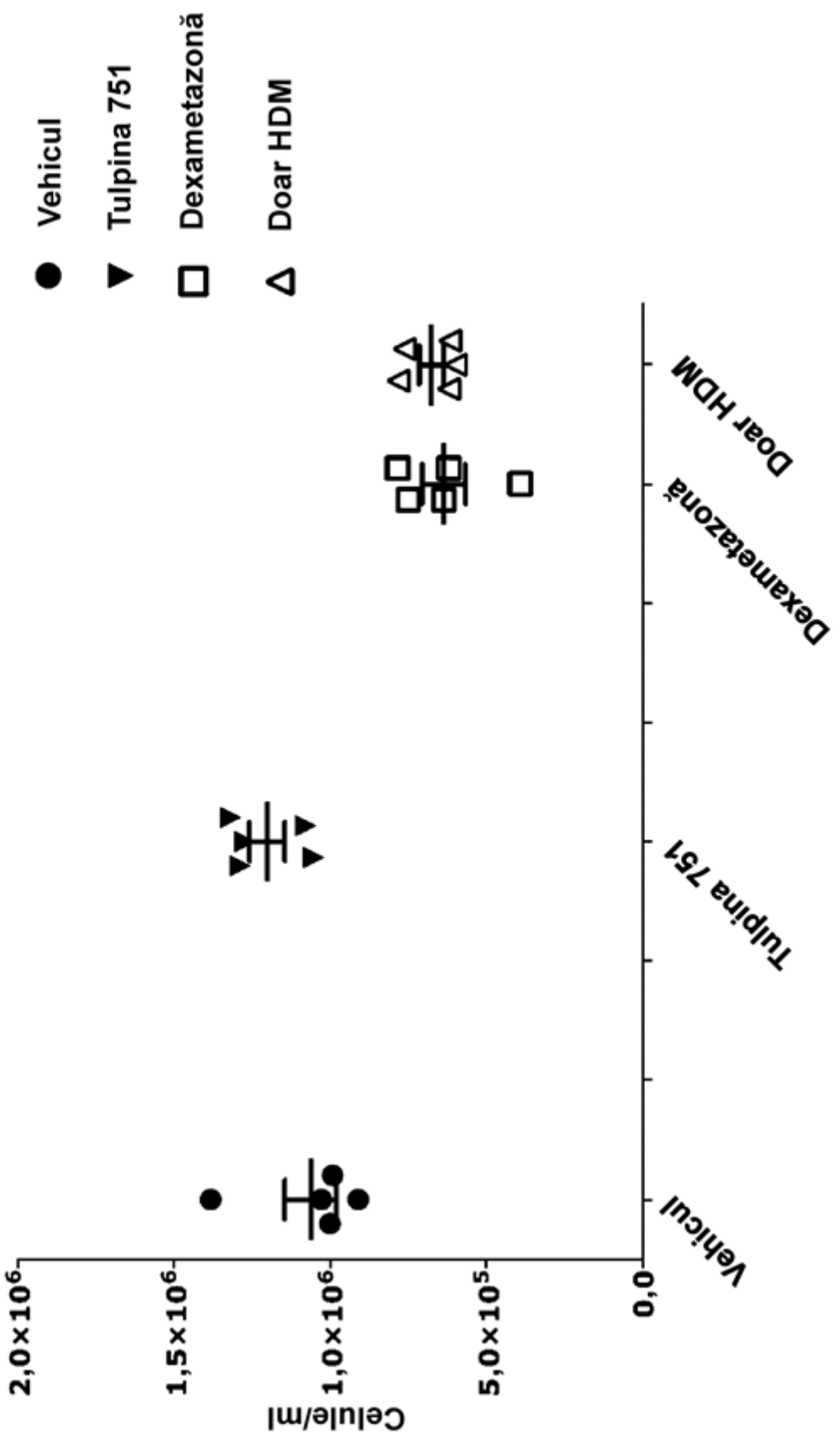


FIG. 2

Numere totale de eozinofile

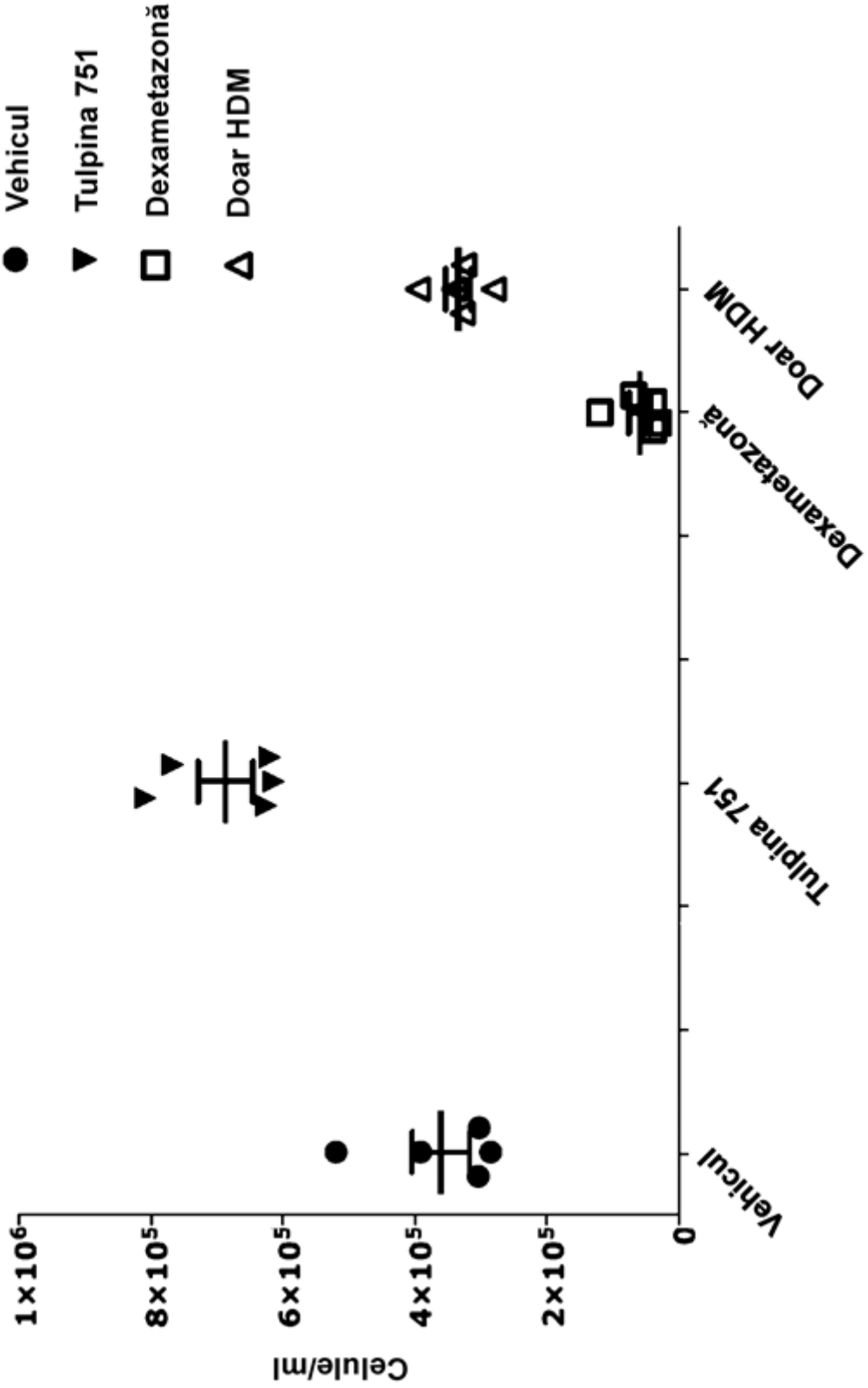


FIG. 3
Procente de eozinofile

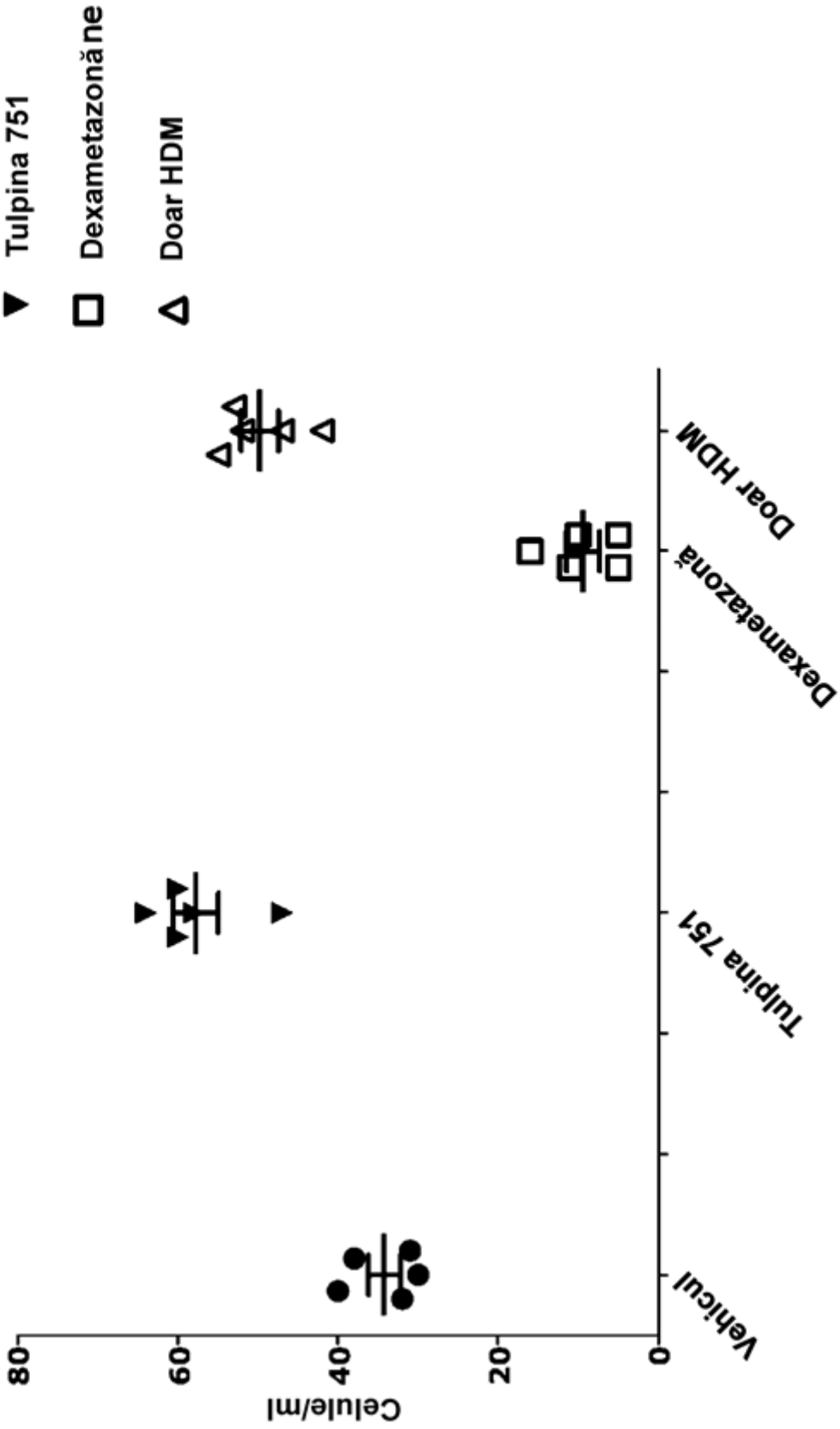
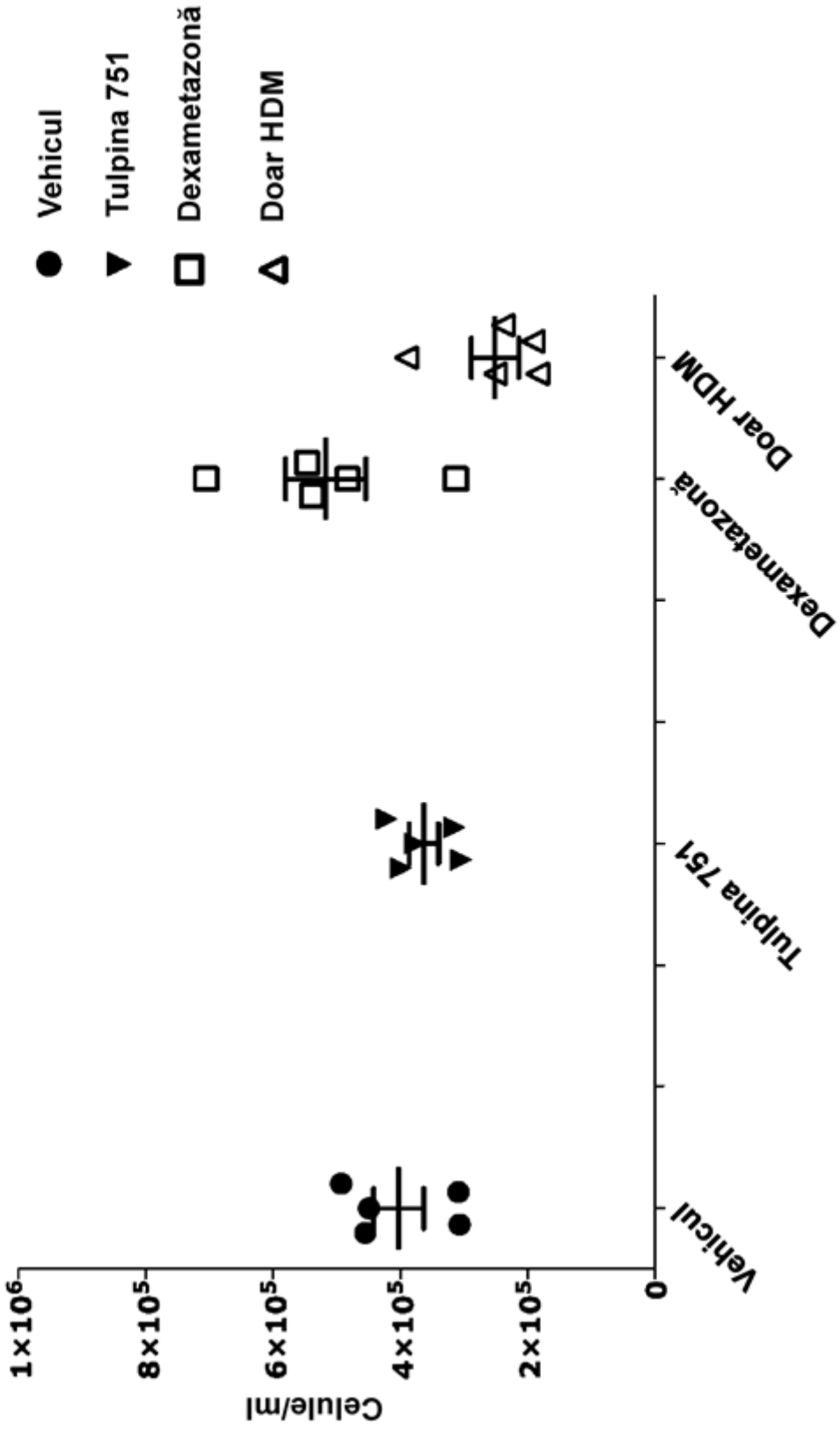


FIG. 4
Numere totale de macrofage



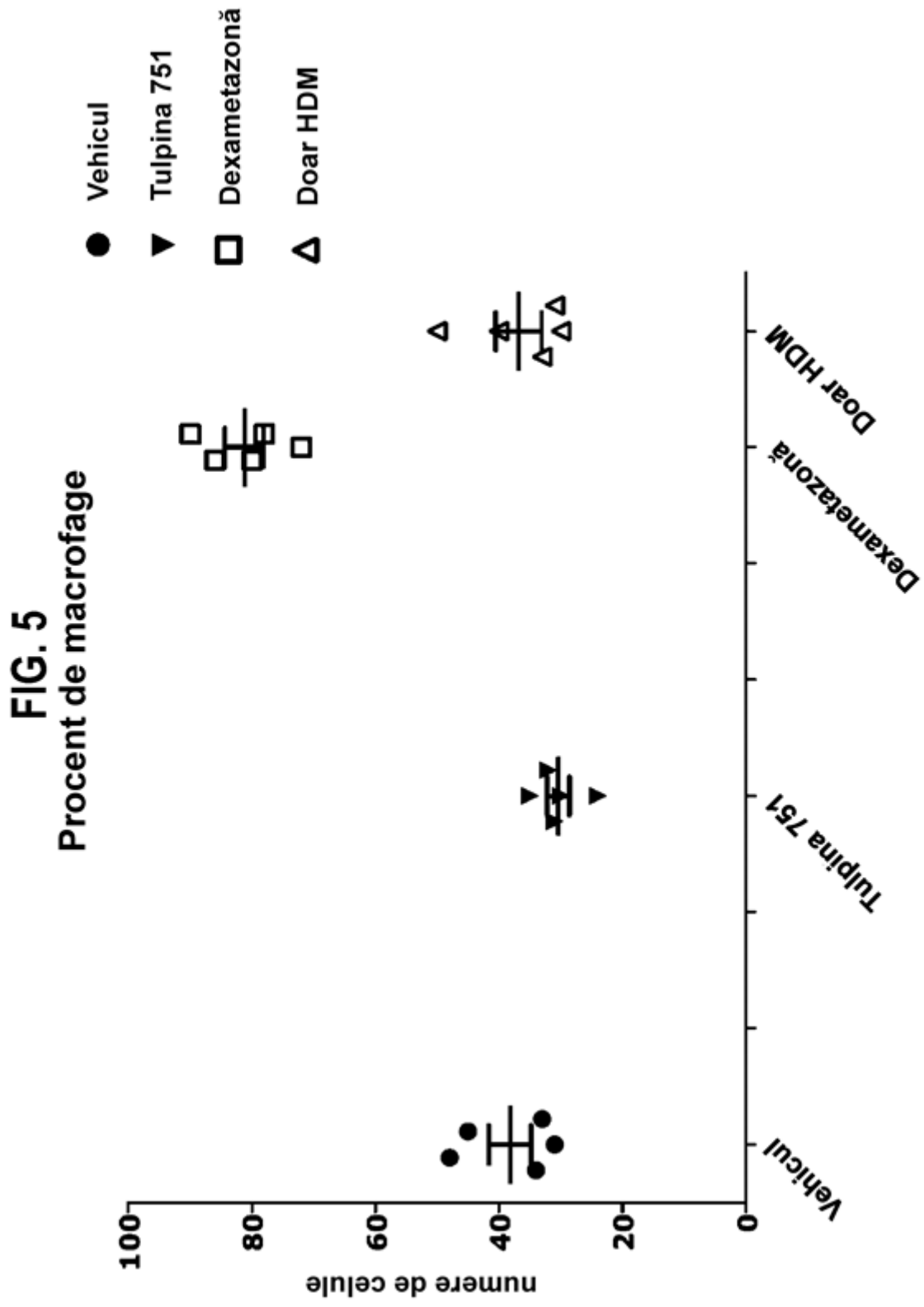


FIG. 5
Procent de macrofage

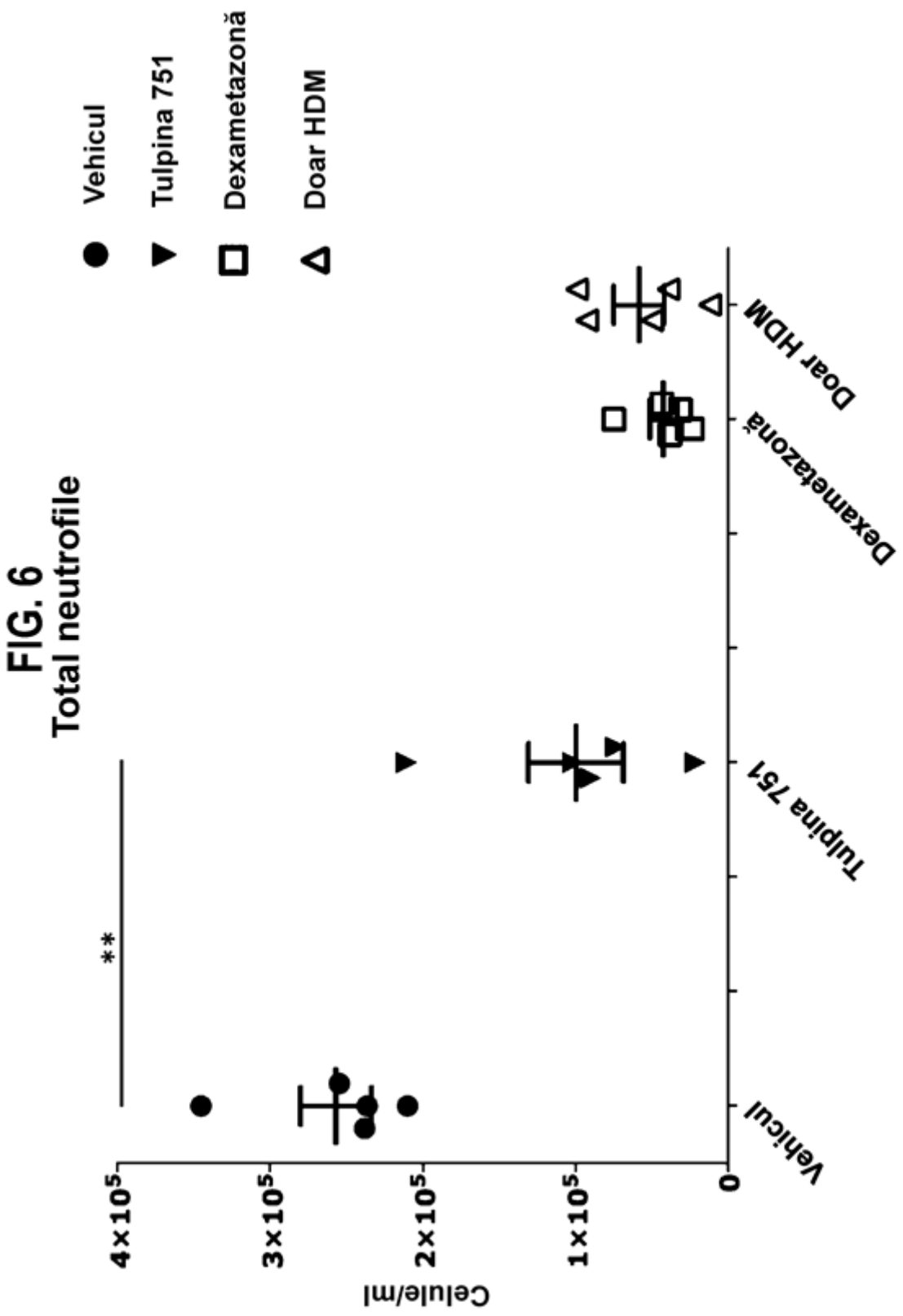


FIG. 6
Total neutrofile
Vehicul
Tulpina 751
Dexametazonă
Doar HDM
**
Celule/ml
4x10^5
3x10^5
2x10^5
1x10^5
0
Vehicul
Tulpina 751
Dexametazonă
Doar HDM

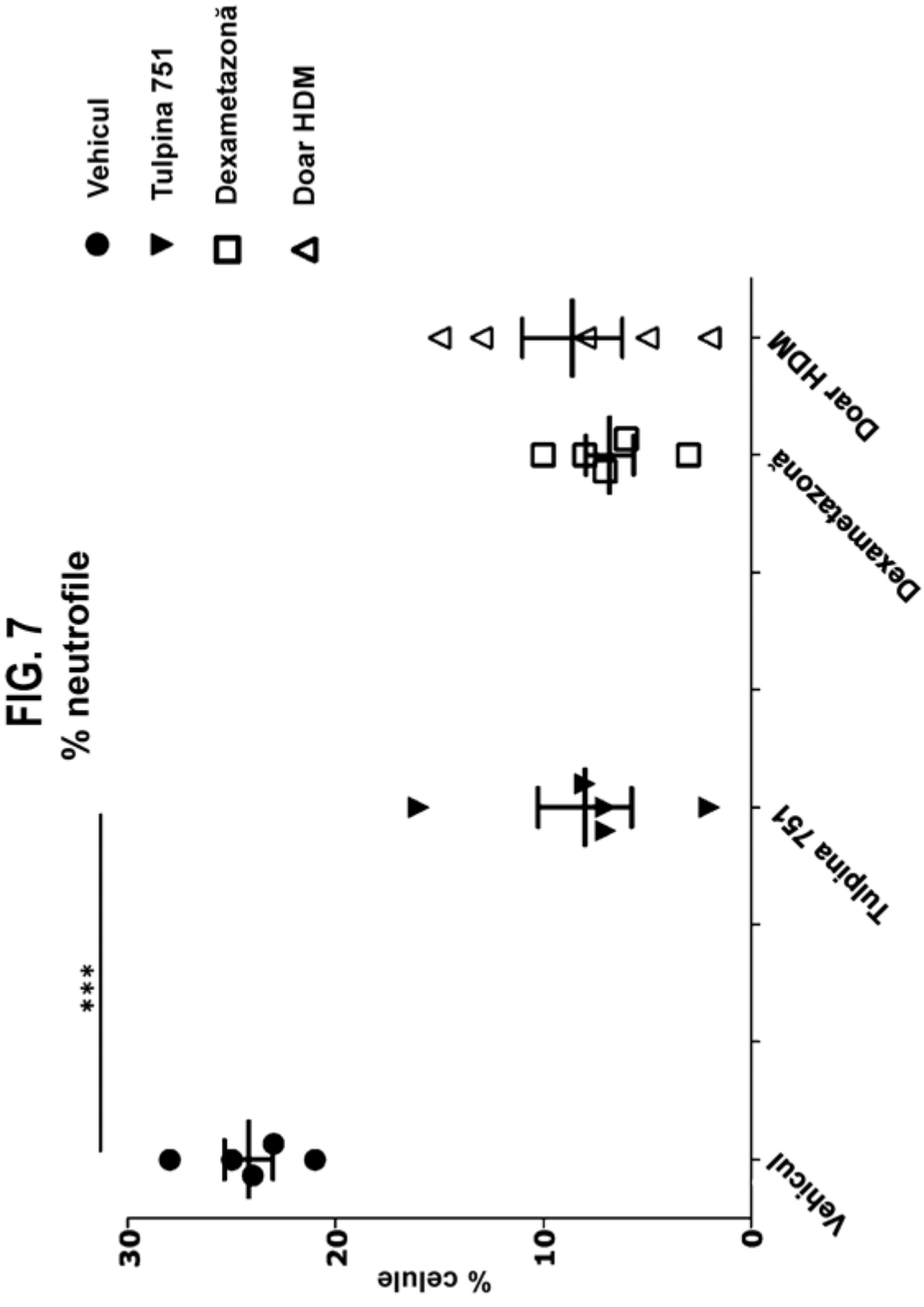


FIG. 7
% neutrofile
***
Vehicul
Tulpina 751
Dexametazonă
Doar HDM
% celule
0
10
20
30
Vehicul
Tulpina 751
Dexametazonă
Doar HDM

FIG. 8
Total limfocite

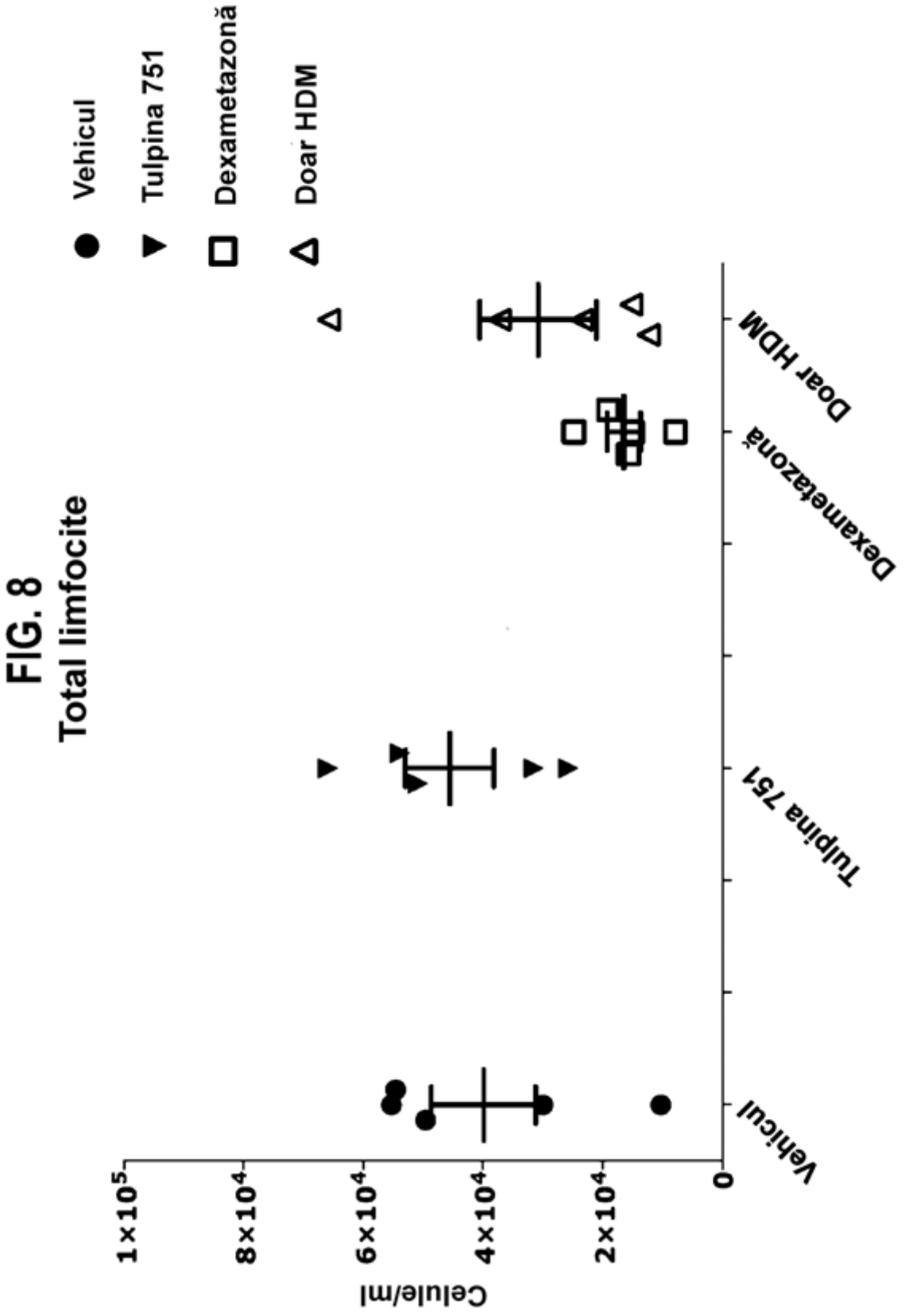


FIG. 9
% limfocite

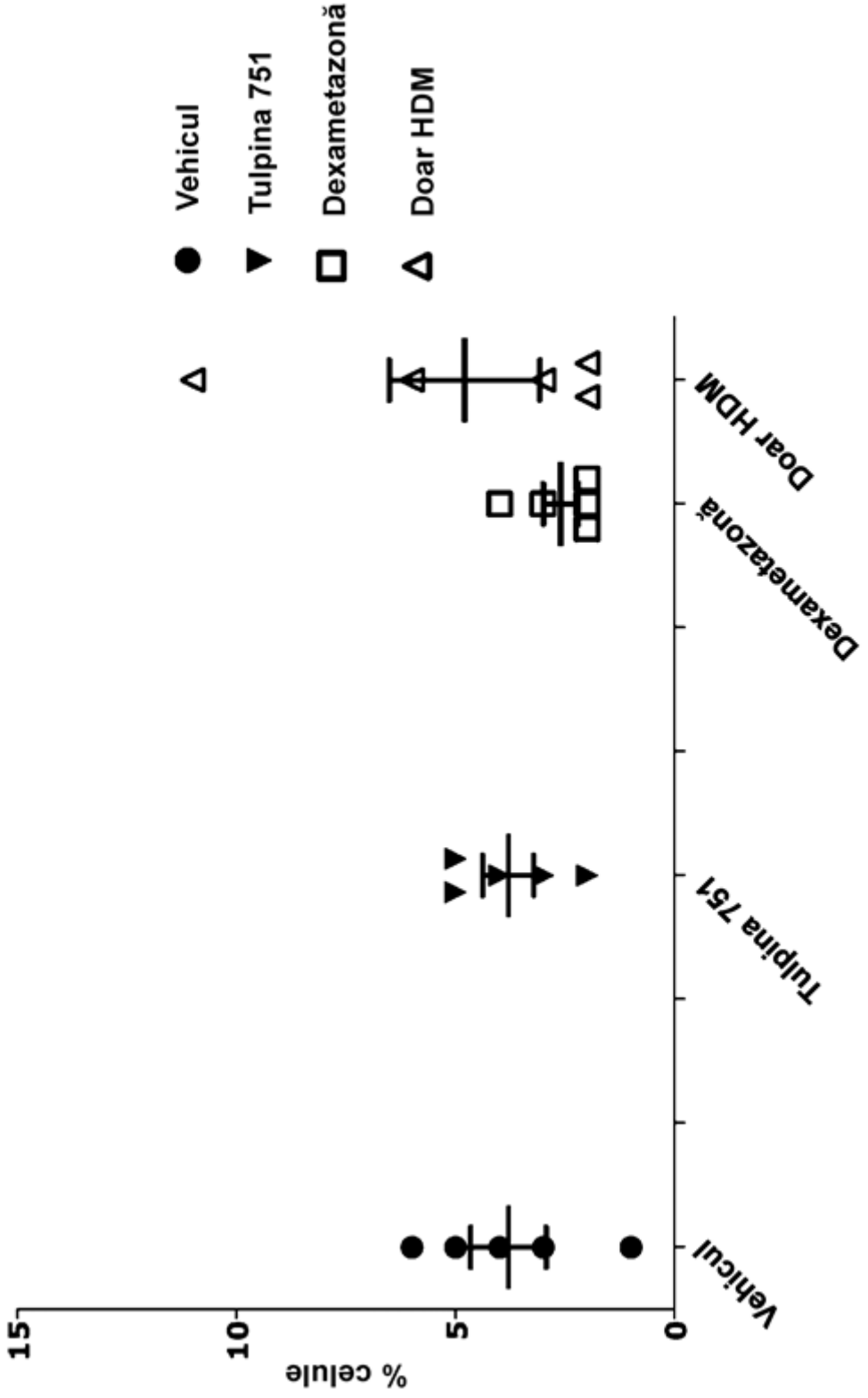


FIG. 10

Numere totale de celule

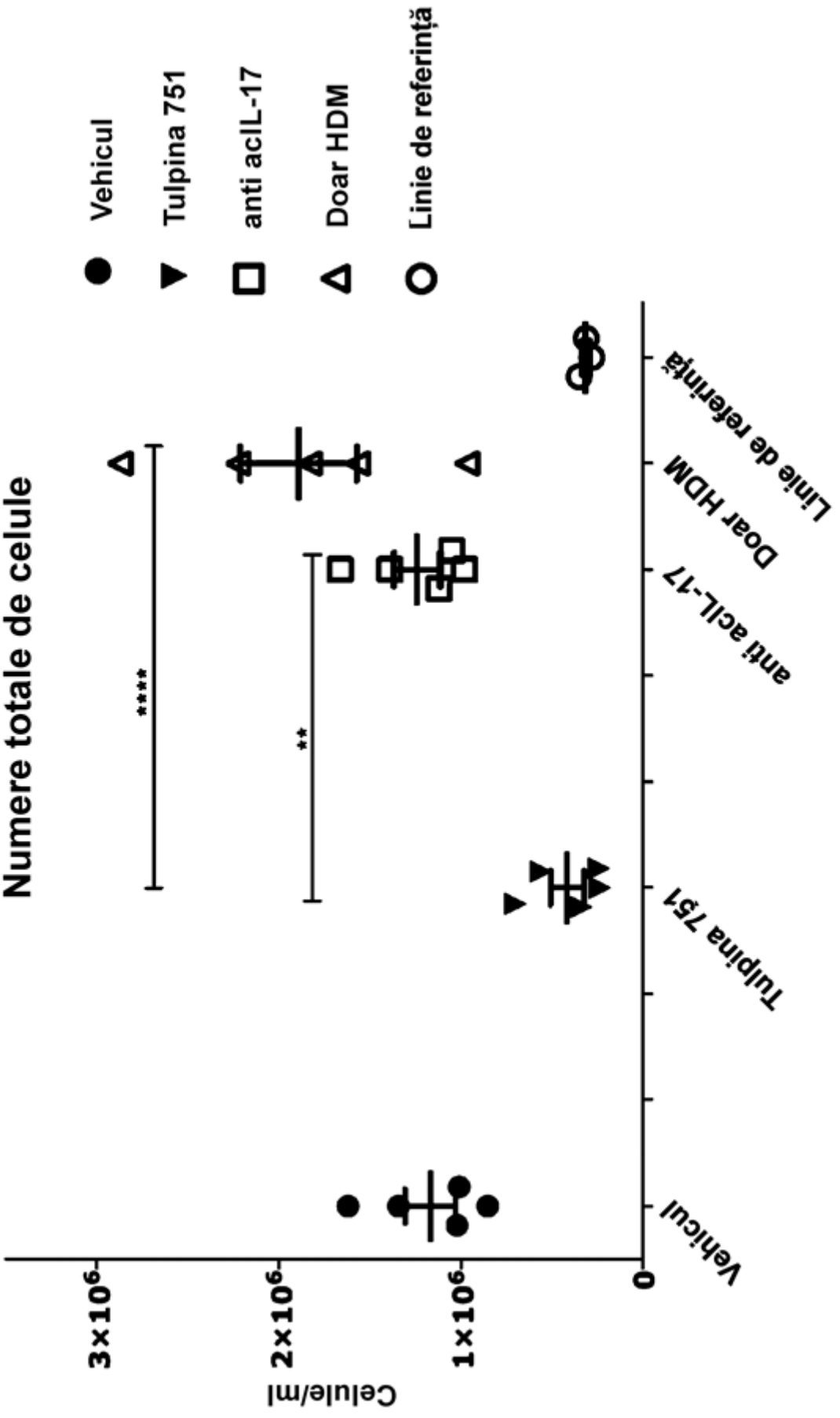


FIG. 11

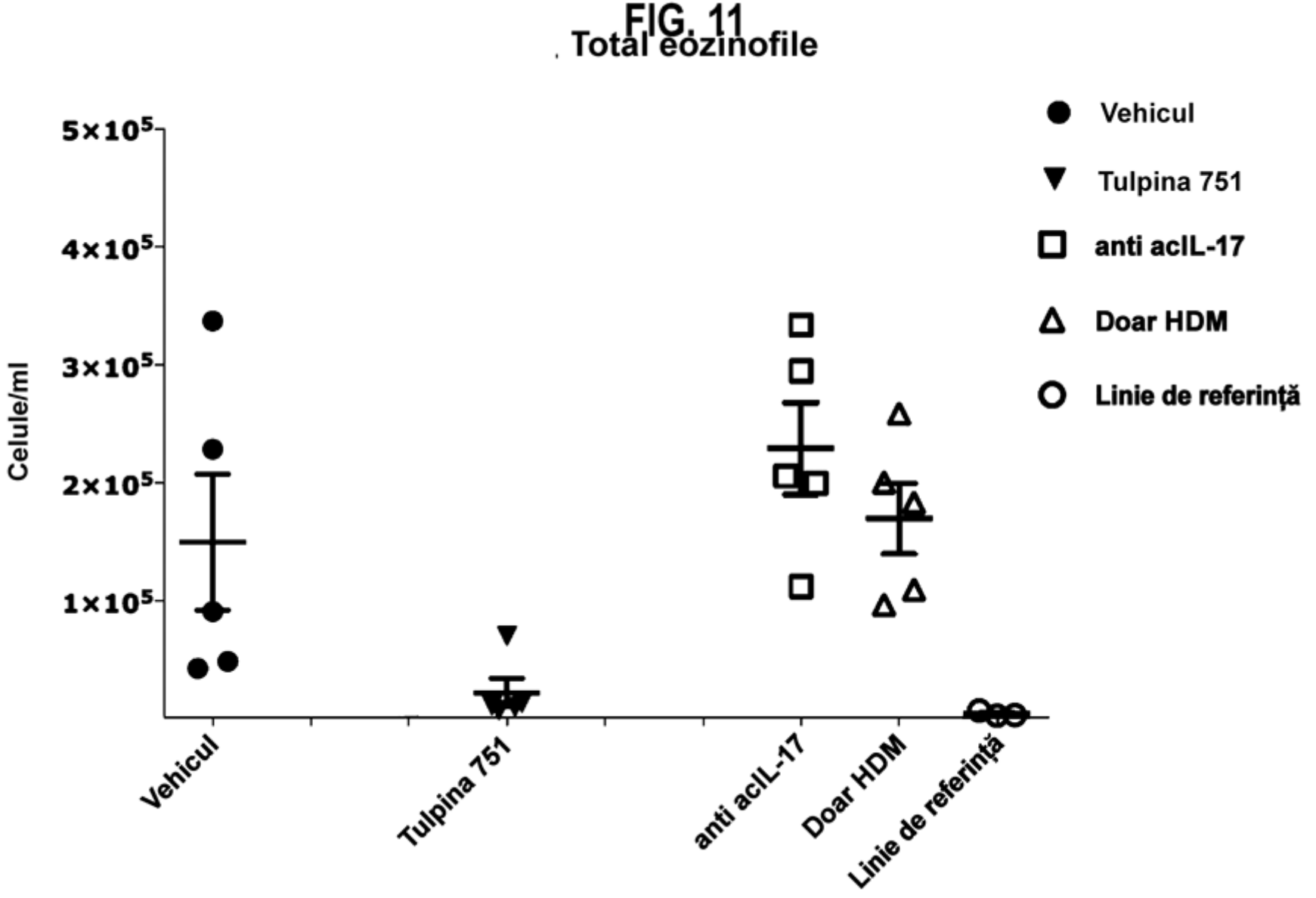


FIG. 12
Procent eozinofile

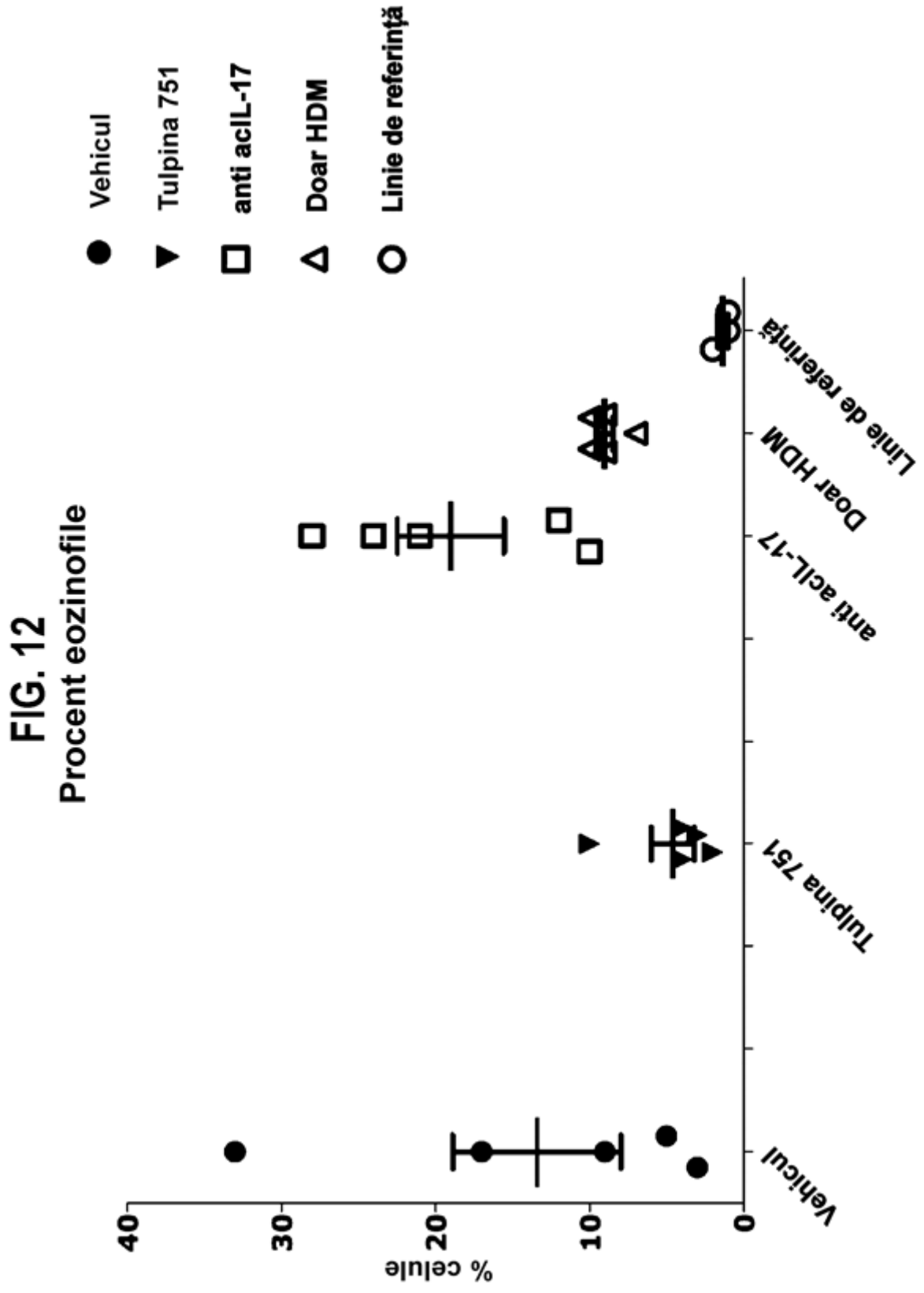
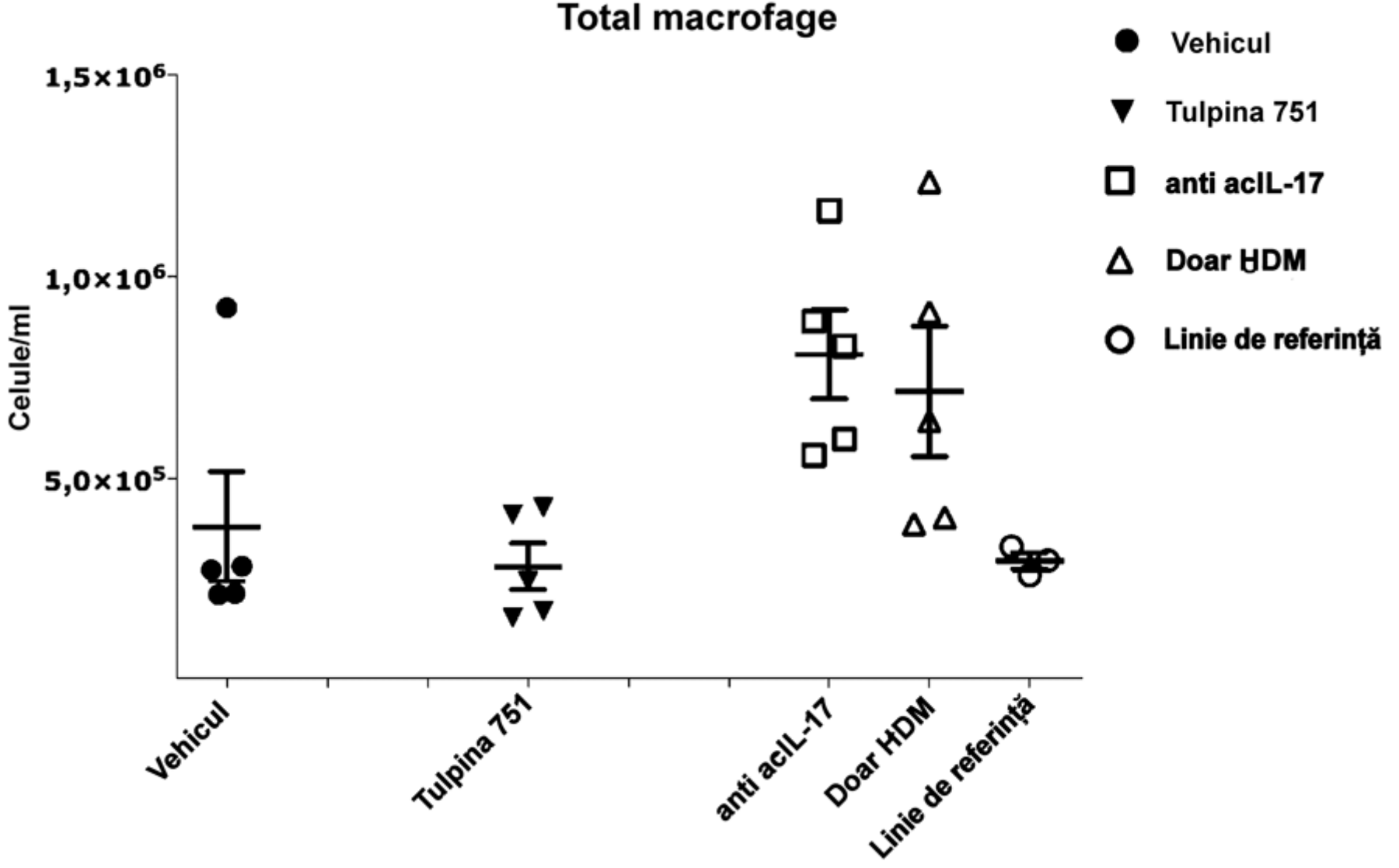


FIG. 13



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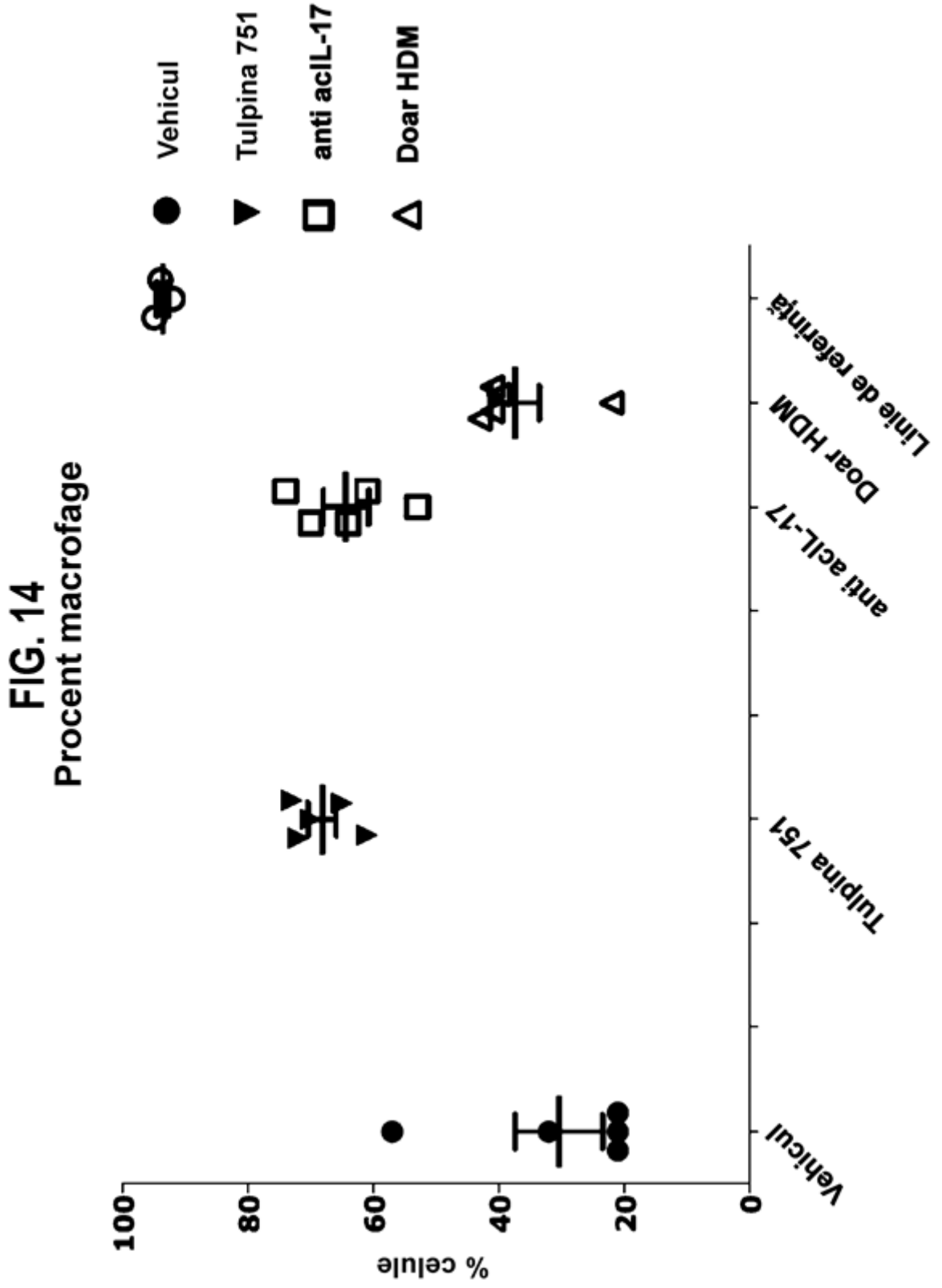


FIG. 14
Procent macrofage
Vehicul
Tulpina 751
anti acIL-17
Doar HDM
% celule
100
80
60
40
20
0
Vehicul
Tulpina 751
anti acIL-17
Doar HDM
Linie de referinţă

FIG. 15
Total neutrofile

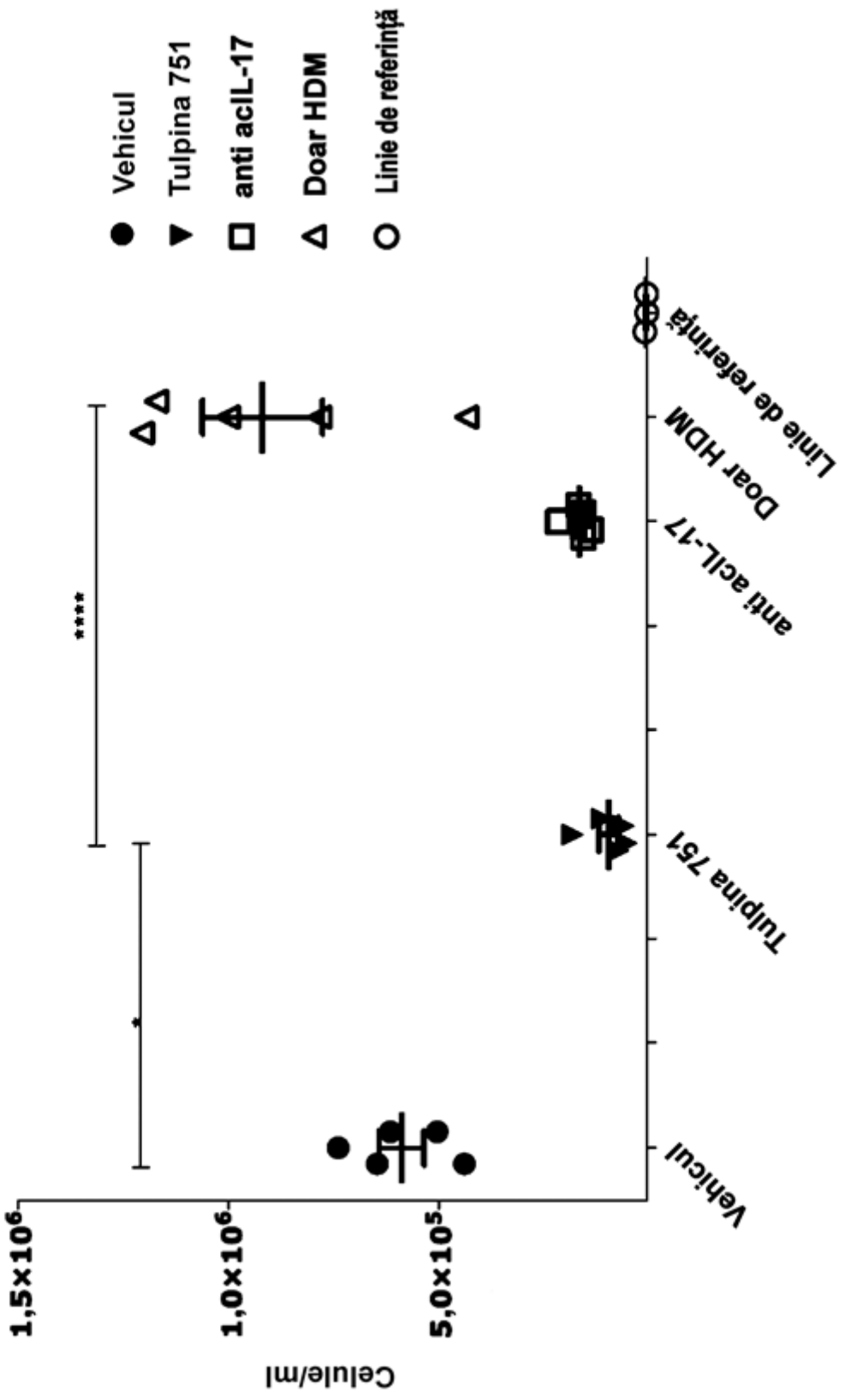


FIG. 16
Procent neutrofile

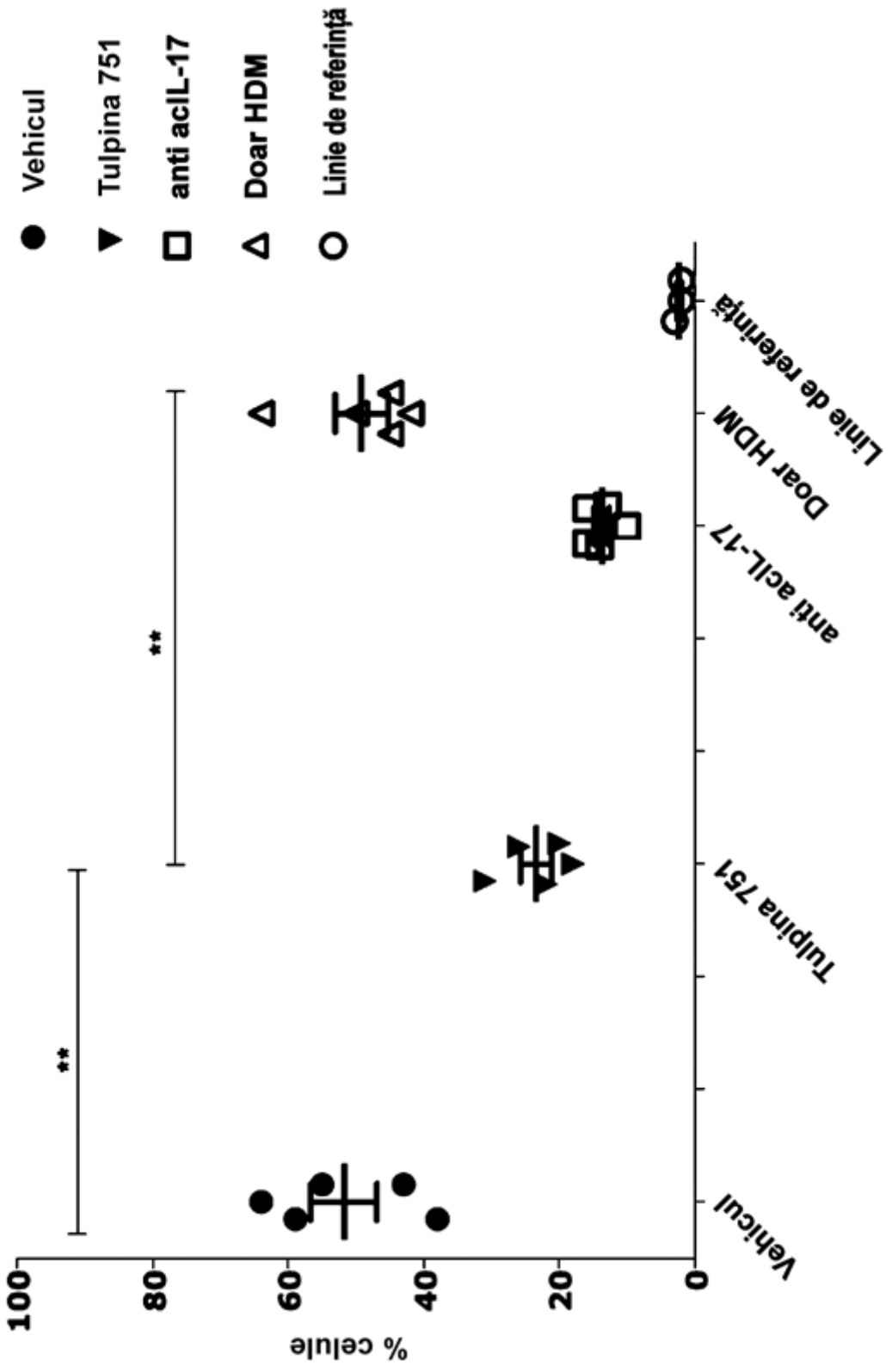
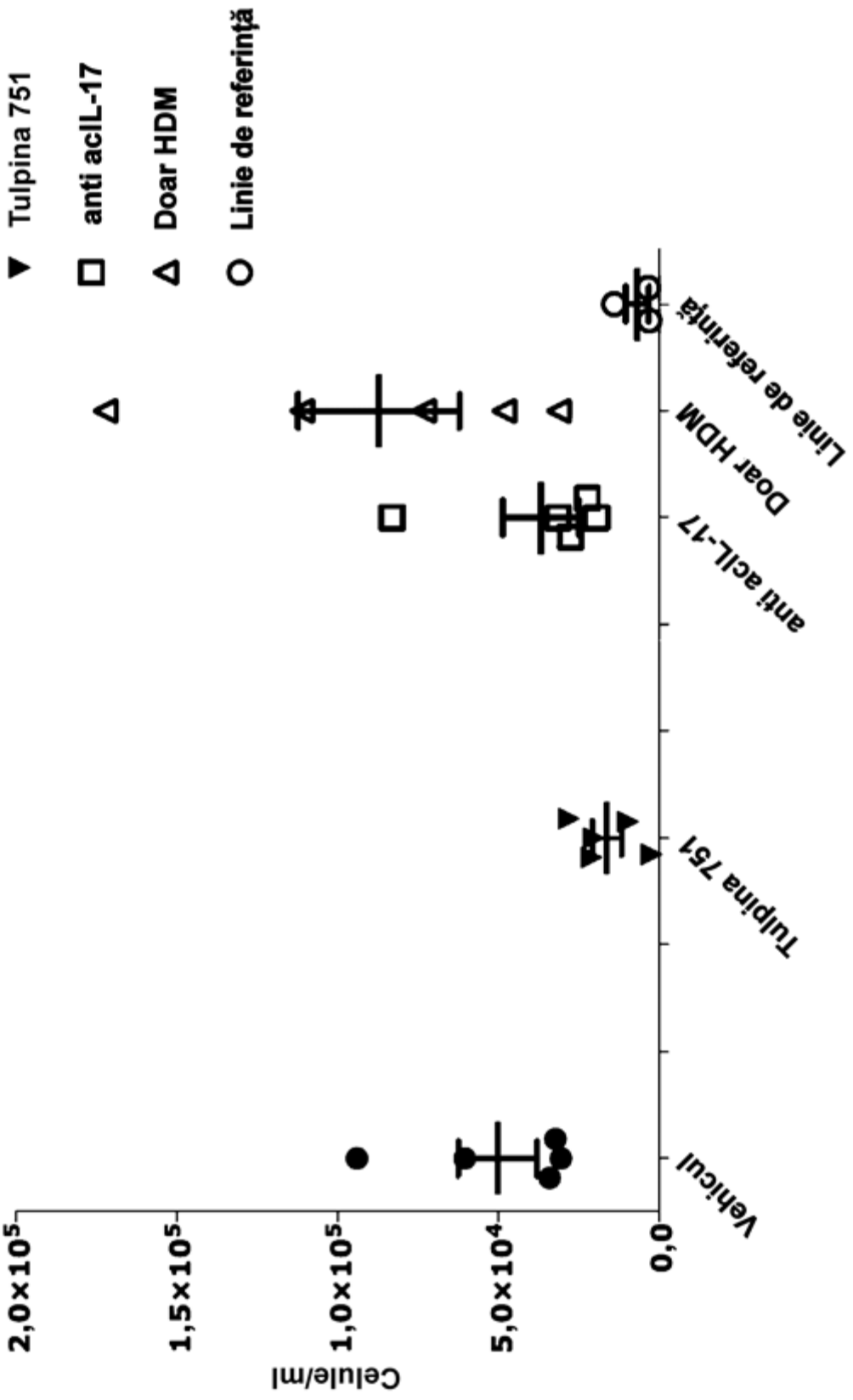


FIG. 17

Total limfocite



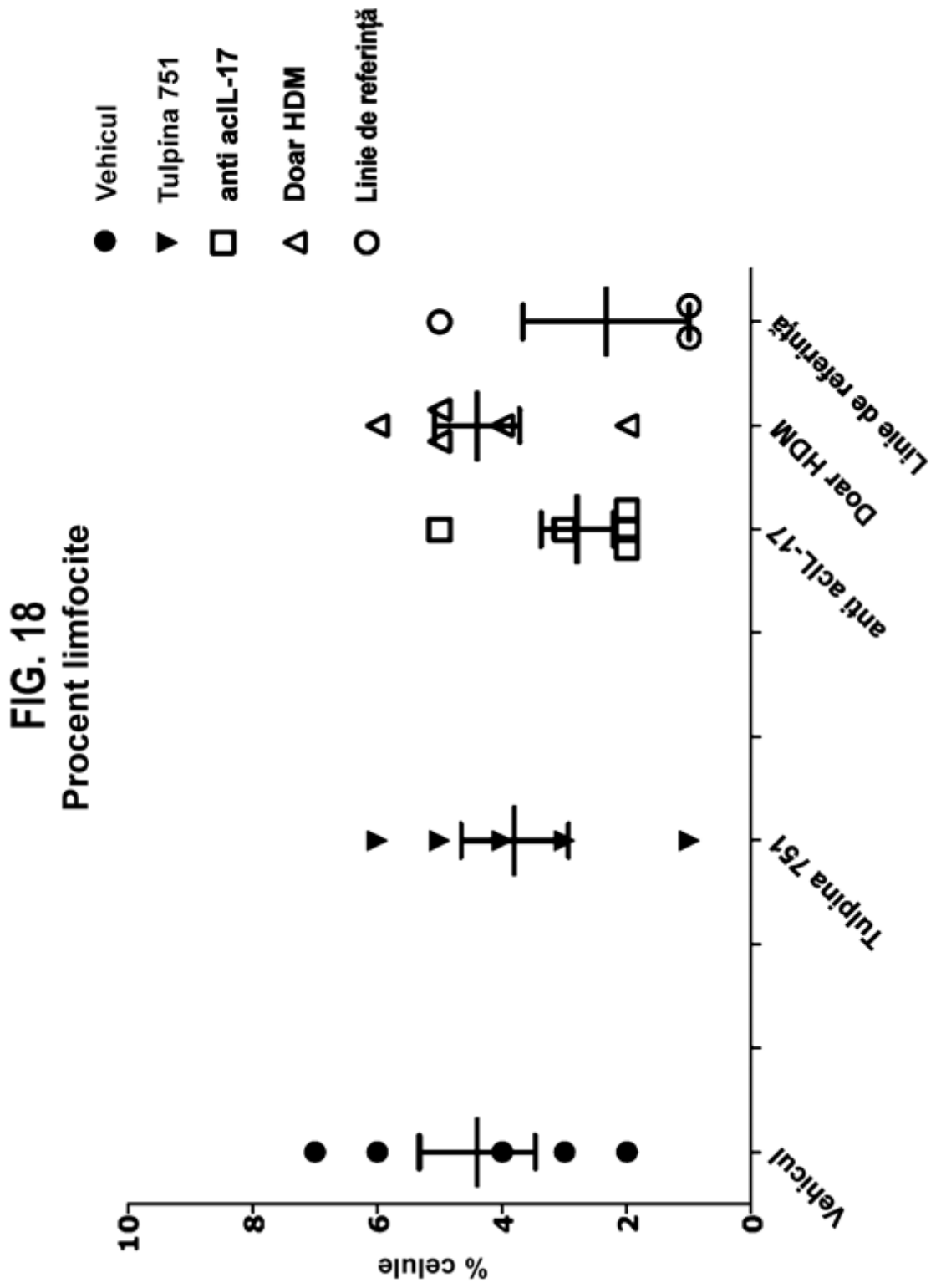


FIG. 18
Procent limfocite

FIG. 19
Mase corporale

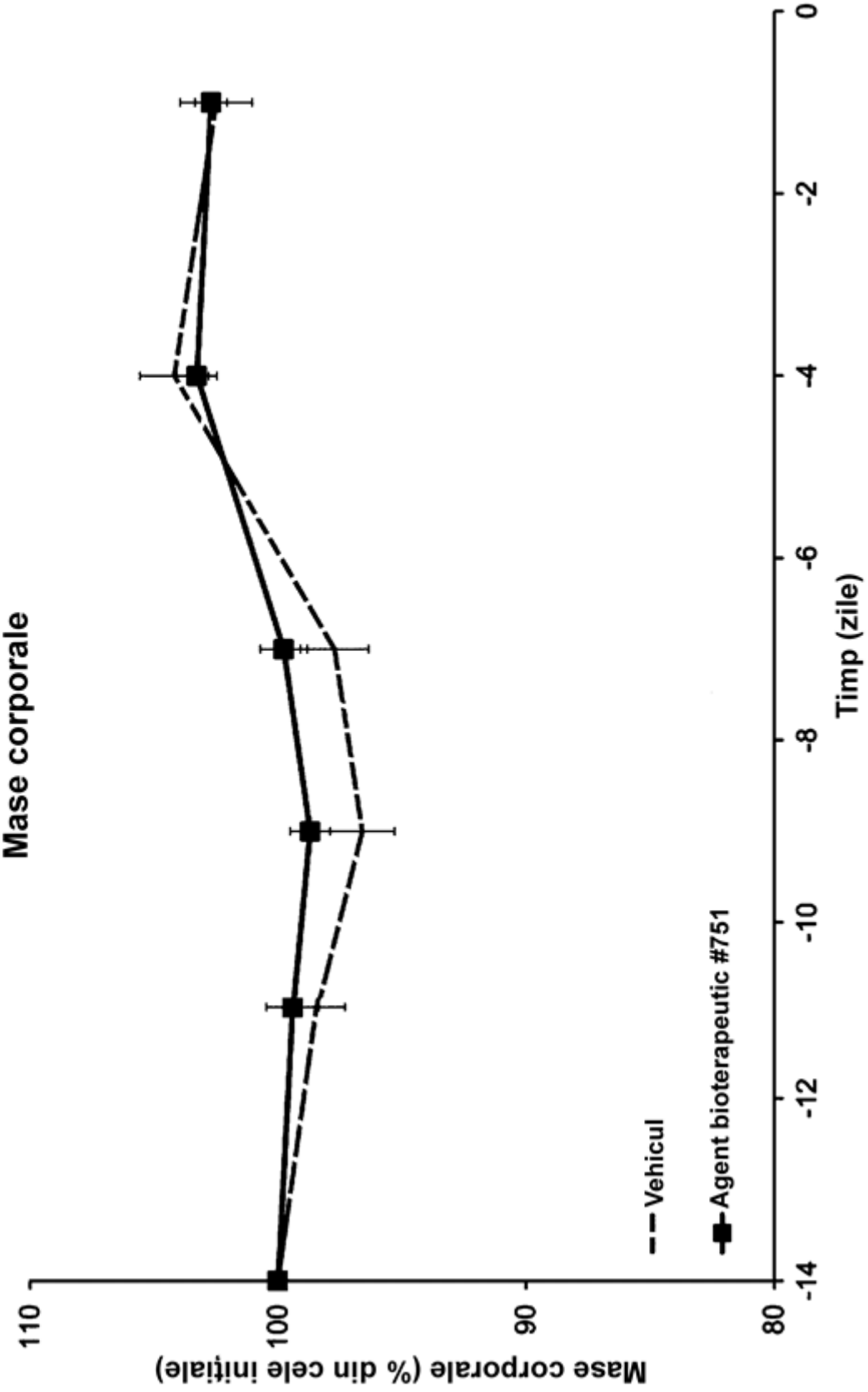


FIG. 20
Mase corporale

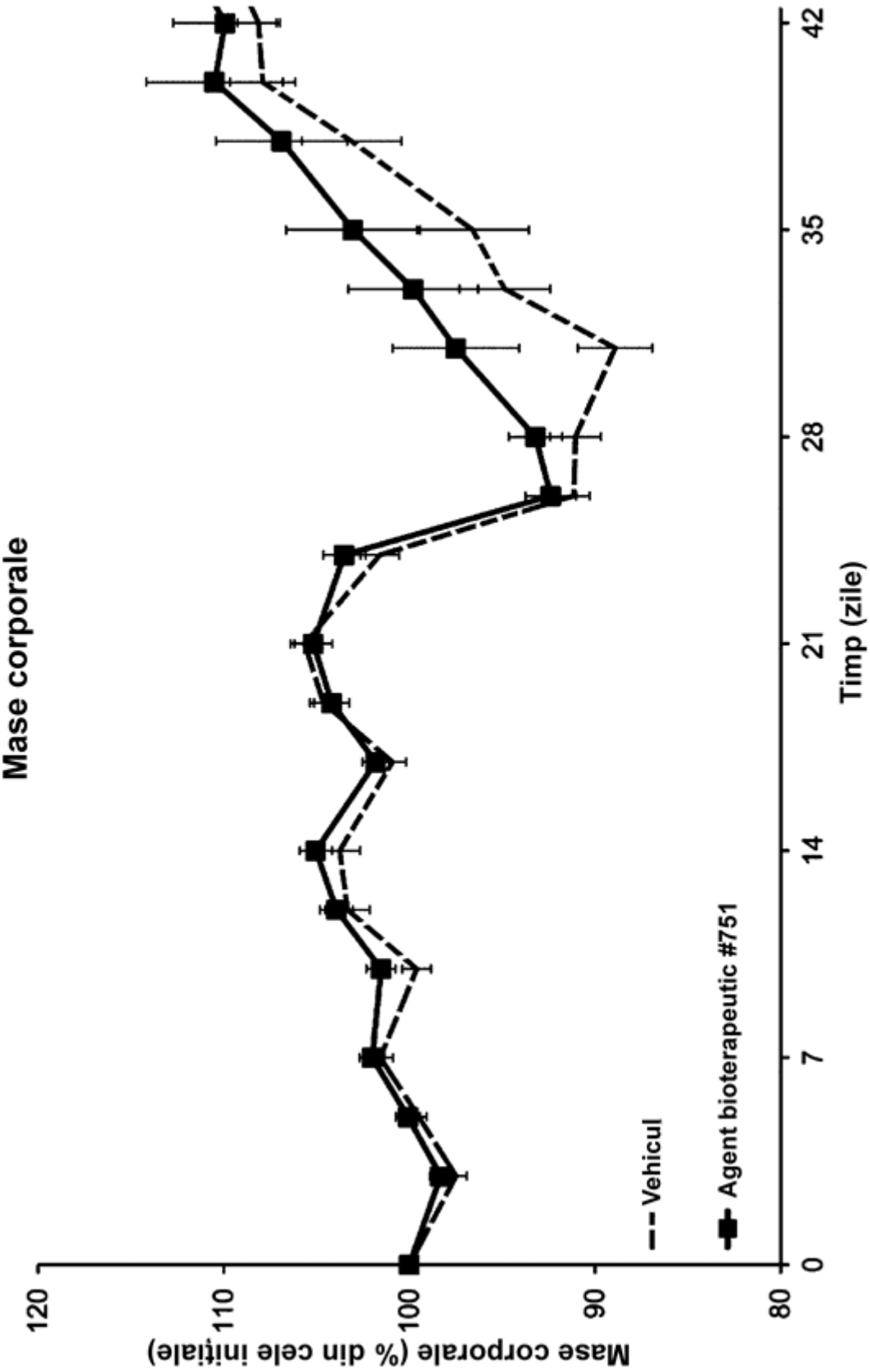


FIG. 21
Scoruri clinice

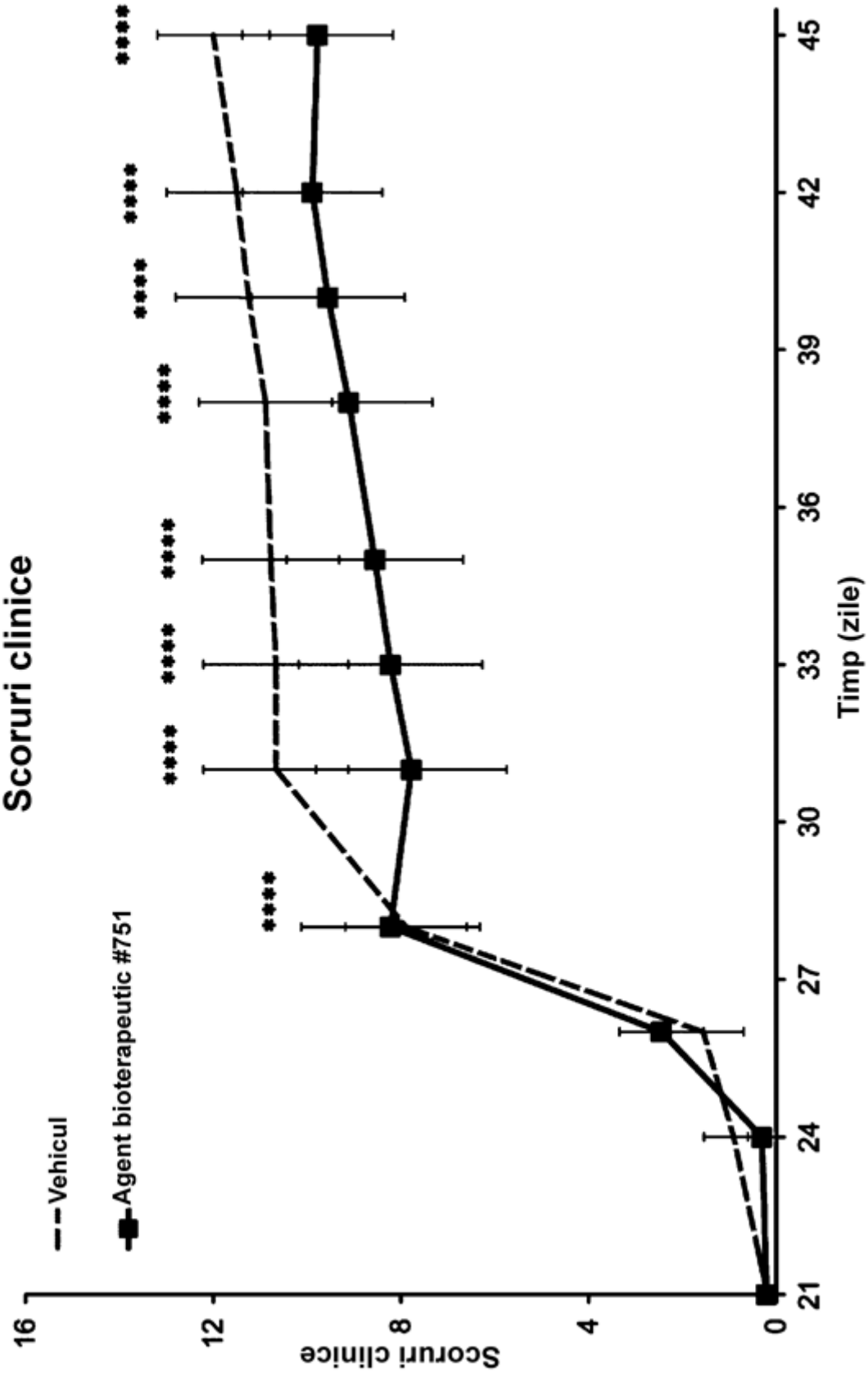


FIG. 22

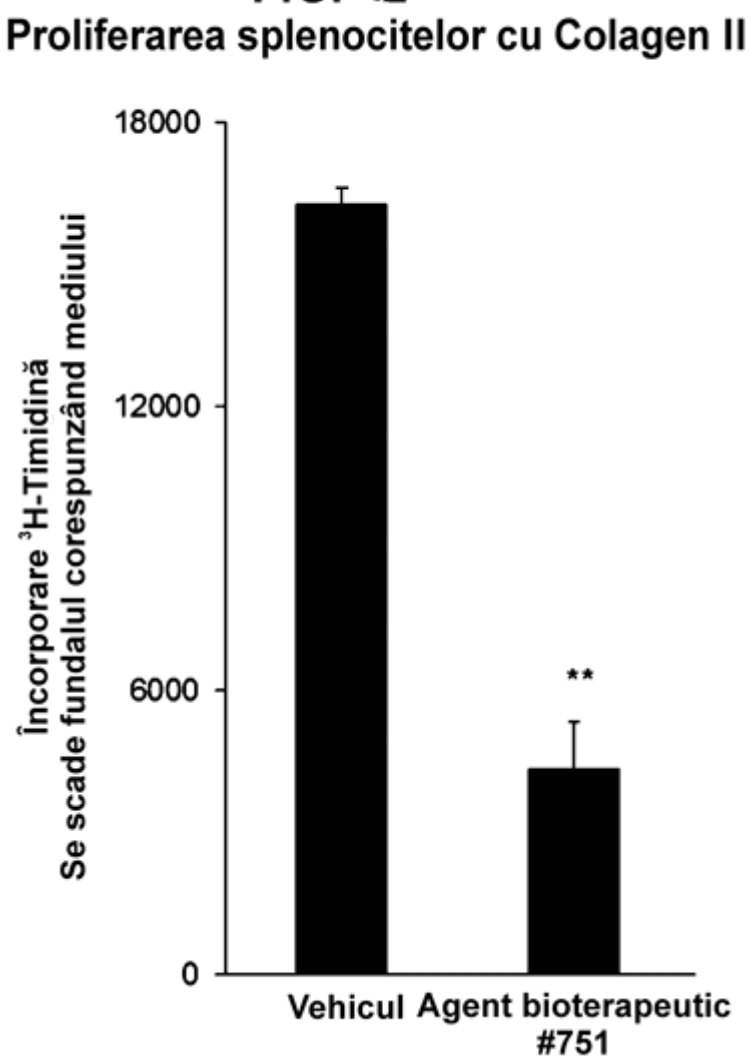


FIG. 23

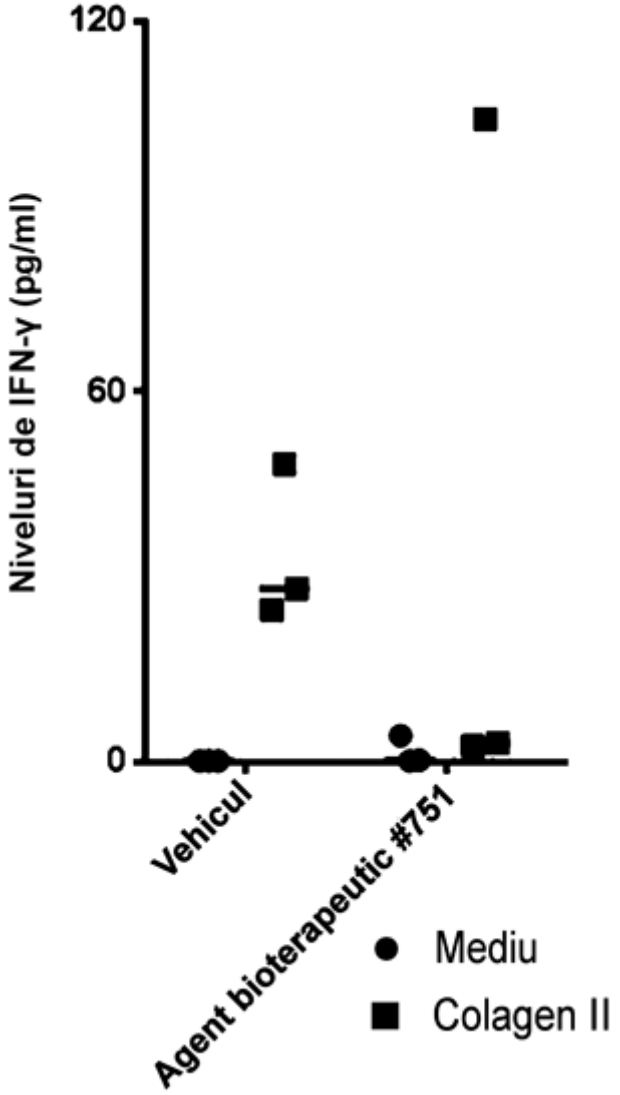


FIG. 24

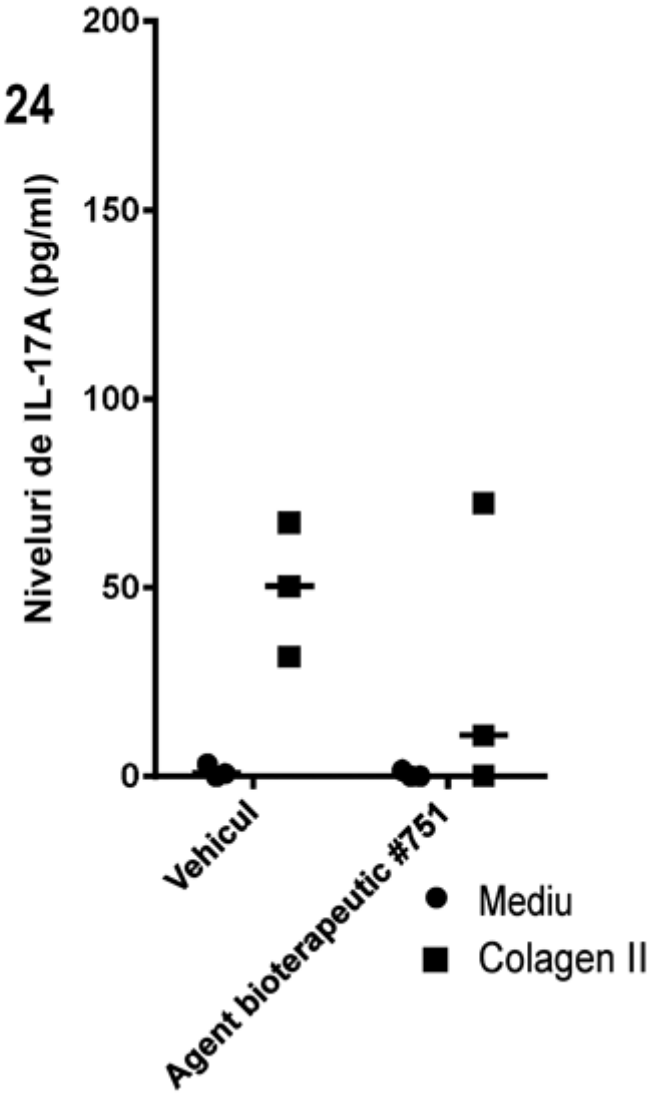


FIG. 25

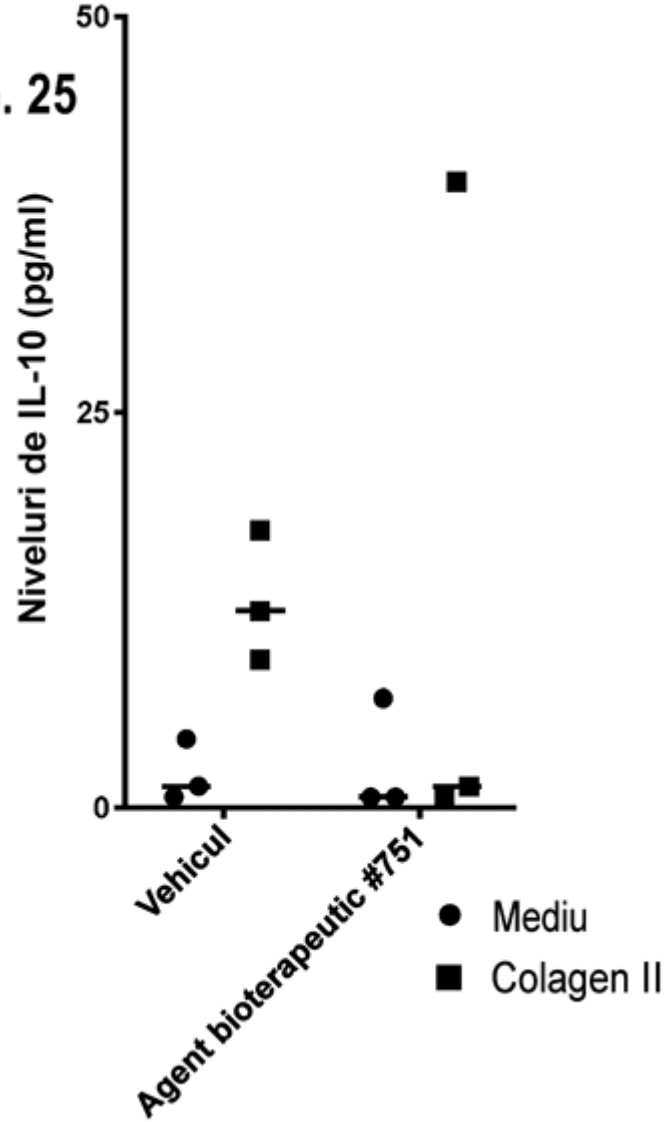


FIG. 26

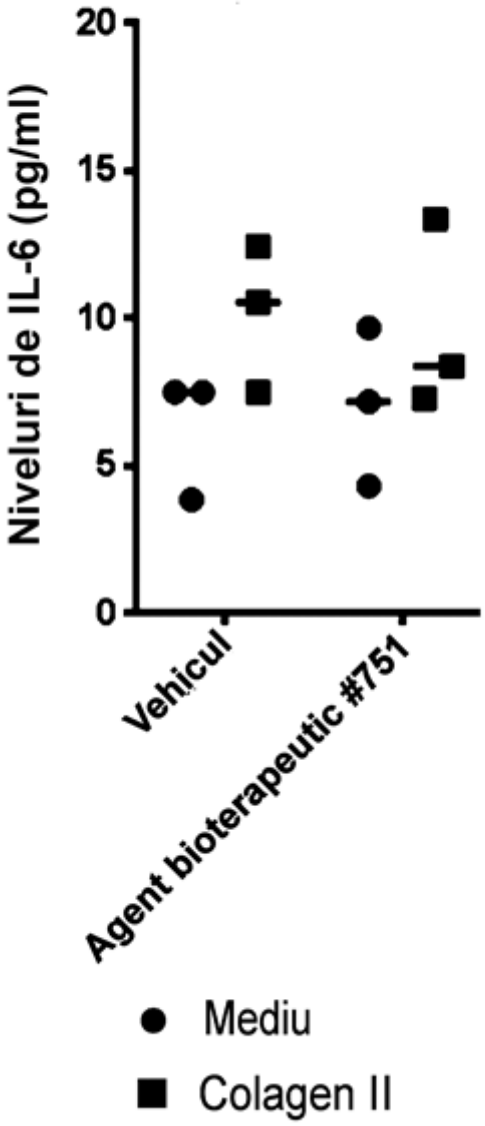

Niveluri de IL-6 (pg/ml)
20
15
10
5
0
Vehicul
Agent bioterapeutic #751
Mediu
Colagen II

FIG 27

Sistem de evaluare histopatologică

Grad	Descriere
Informație	
0	**Articulație normală.**
1	**Hiperplazie sinovială ușoară cu inflamație dominată de neutrofile. Numere mici de neutrofile și macrofage în spațiul articular.**
2	**Hiperplazie sinovială moderată cu inflamație marcată implicînd atât neutrofile cât și macrofage. Neutrofile și macrofage în spațiul articular; pot exista unele deșeuri tisulare necrotice.**
3	**Hiperplazie sinovială cu inflamație marcată implicînd atât neutrofile cât și macrofage. Pierderi ale căptușelii de sinoviocite. Inflamația se poate extinde de la sinovium către țesutul înconjurător, incluzând mușchiul. Numeroase neutrofile și macrofage în spațiul articular, împreună cu deșeuri tisulare necrotice semnificative.**
Distrugerea cartilajului articular	
0	**Articulație normală.**
1	**Cartilajul articular prezintă o ușoară schimbare degenerativă. Formarea timpurie de pannus poate fi prezentă periferic.**
2	**Cartilajul articular prezintă schimbare degenerativă moderată și pierdere focală. Formarea de pannus este prezentă focal.**
3	**Întrerupere și pierdere semnificativă a cartilajului.**
Distrugerea osului metafizeal de bază	
0	**Articulație normală.**
1	**Fără schimbare a osului metafizeal.**
2	**Poate exista necroză focală sau fibroză a osului metafizeal.**
3	**Întrerupere sau colaps al osului metafizeal. Inlamație, necroză sau fibroză extensive care se extind în spațiul medular al metafizei.**

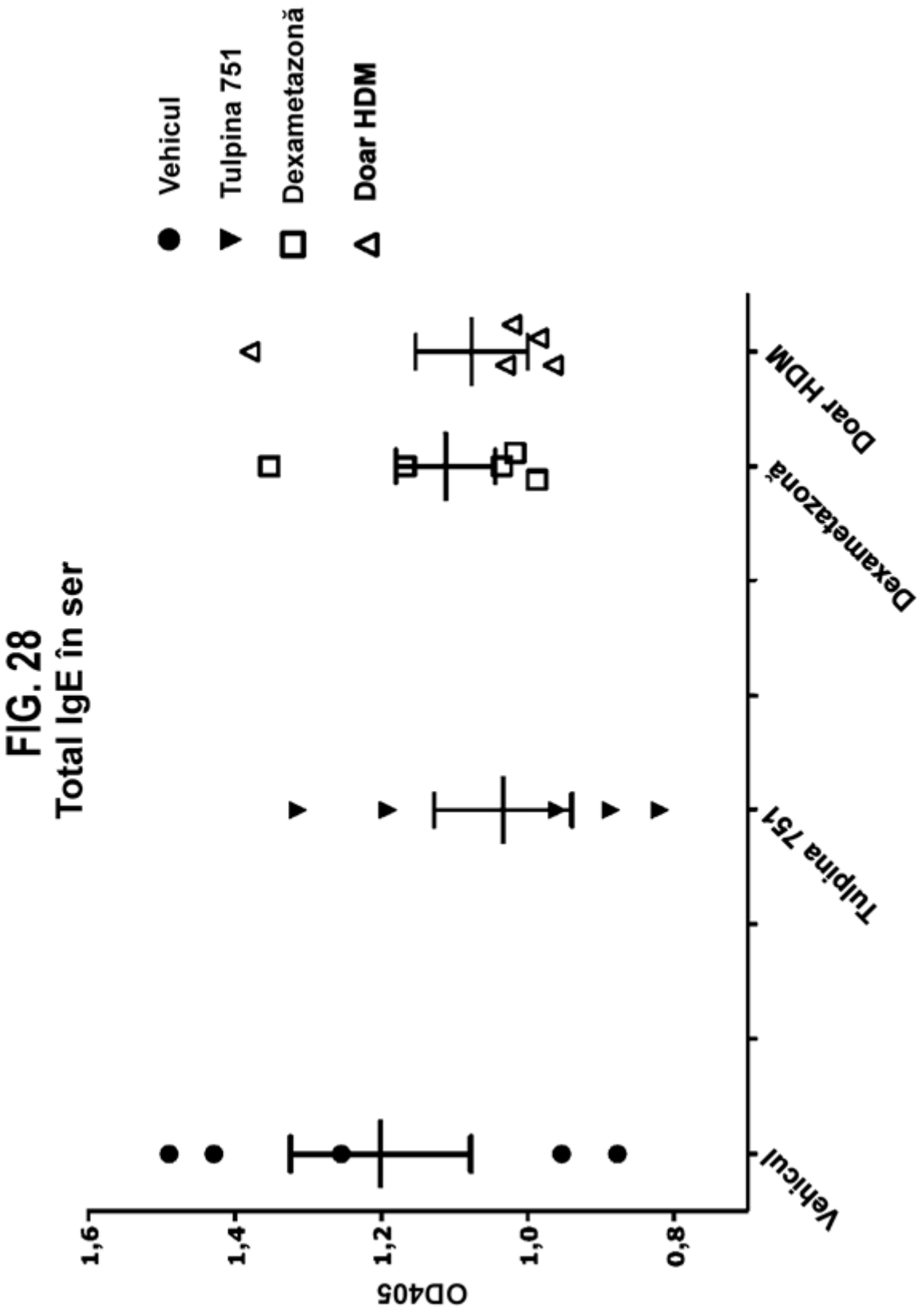


FIG. 28
Total IgE în ser

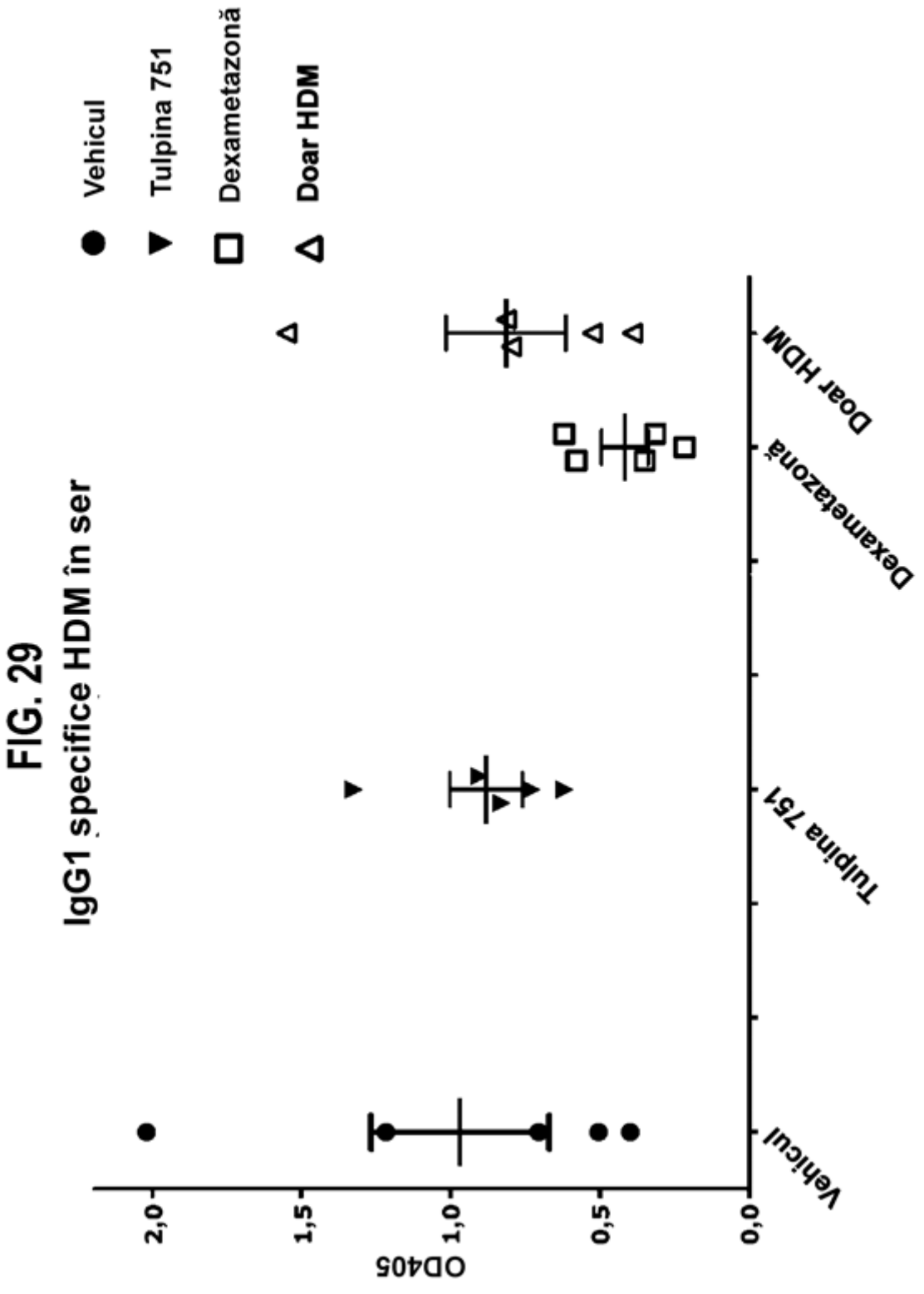


FIG. 29
IgG1 specifice HDM în ser

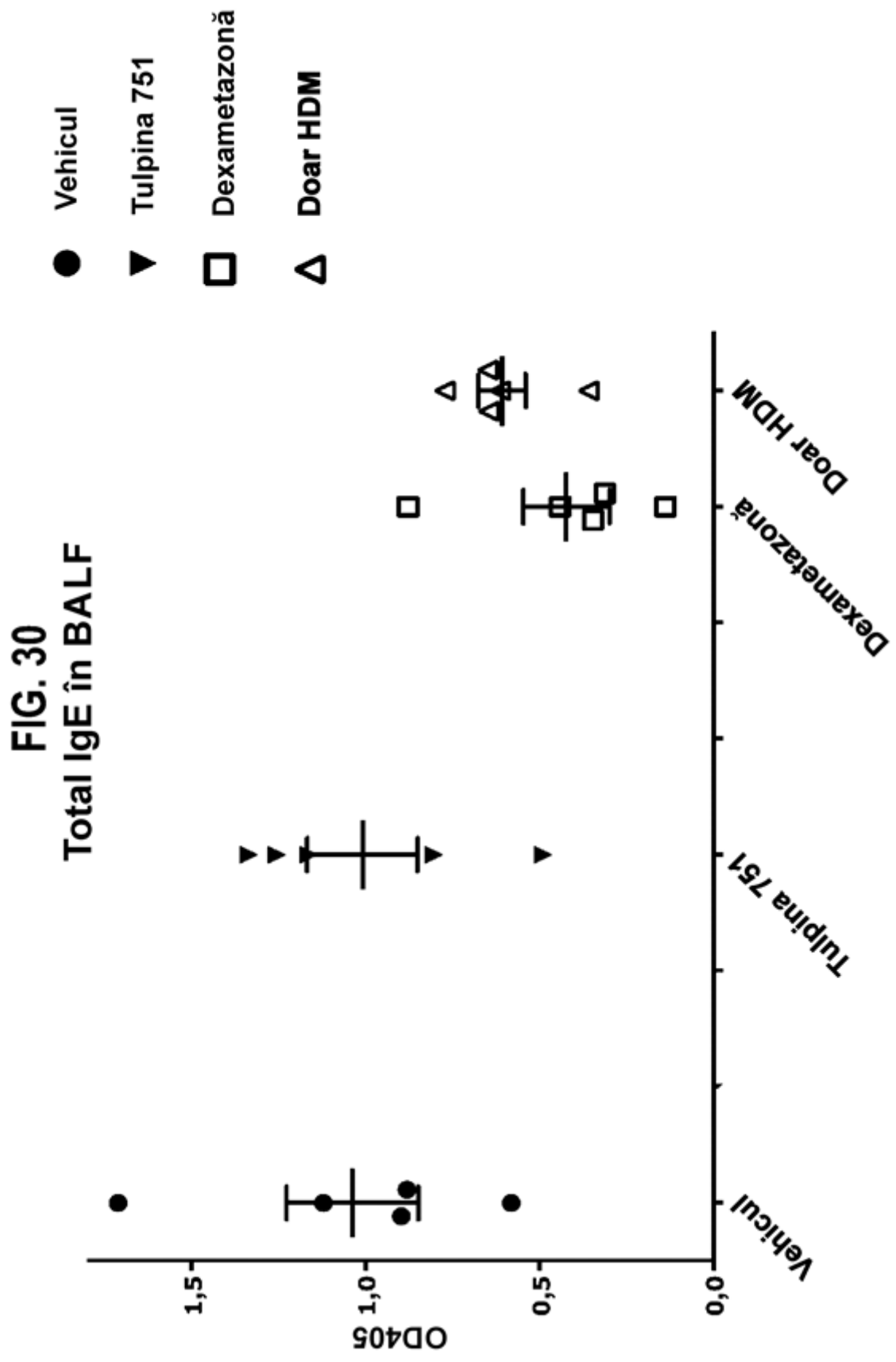


FIG. 30
Total IgE în BALF

FIG. 31
IgG1 specifică HDM în BALF

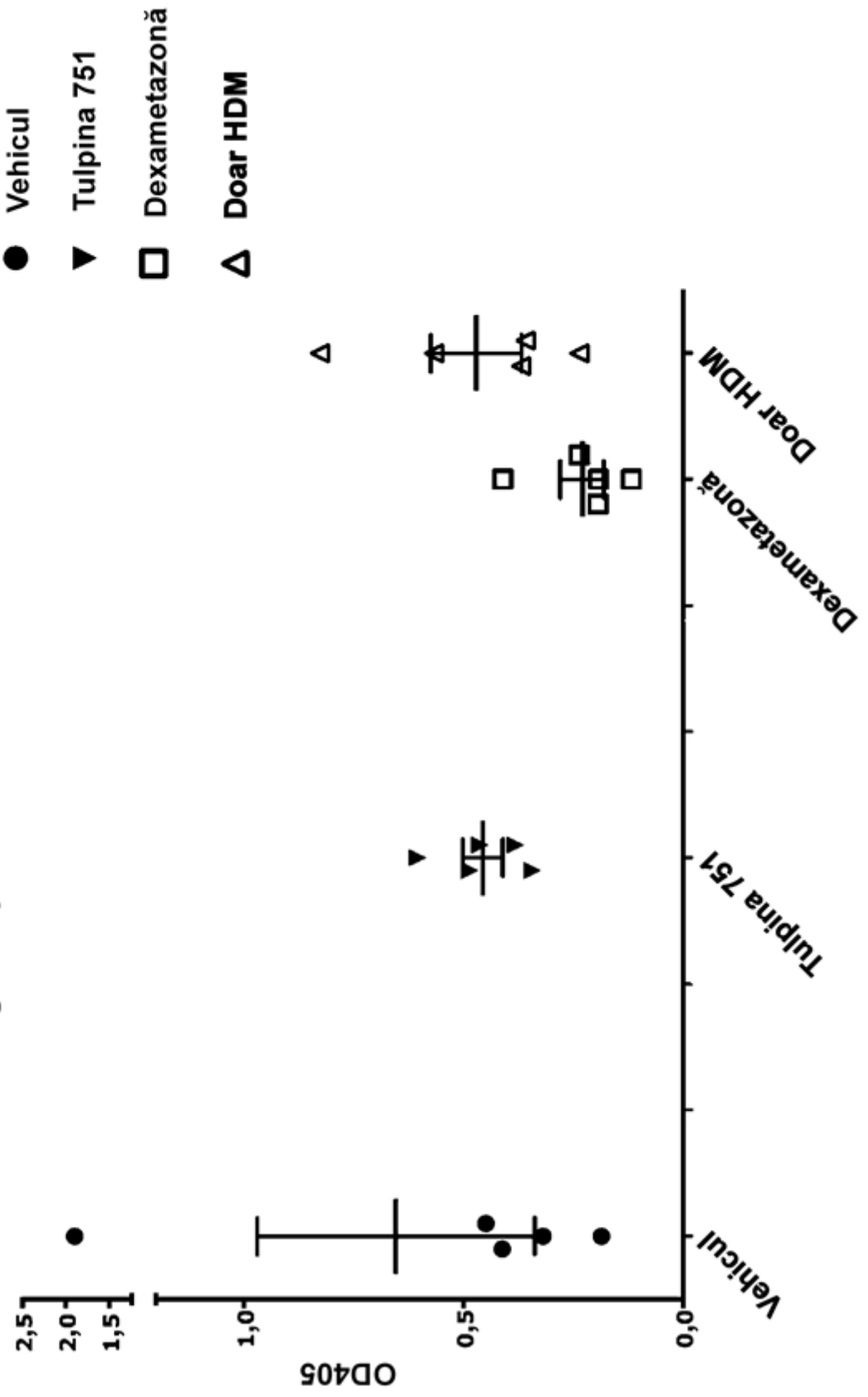


FIG. 32 Analiza histologică - scor mediu de înfiltare peribrohiolară

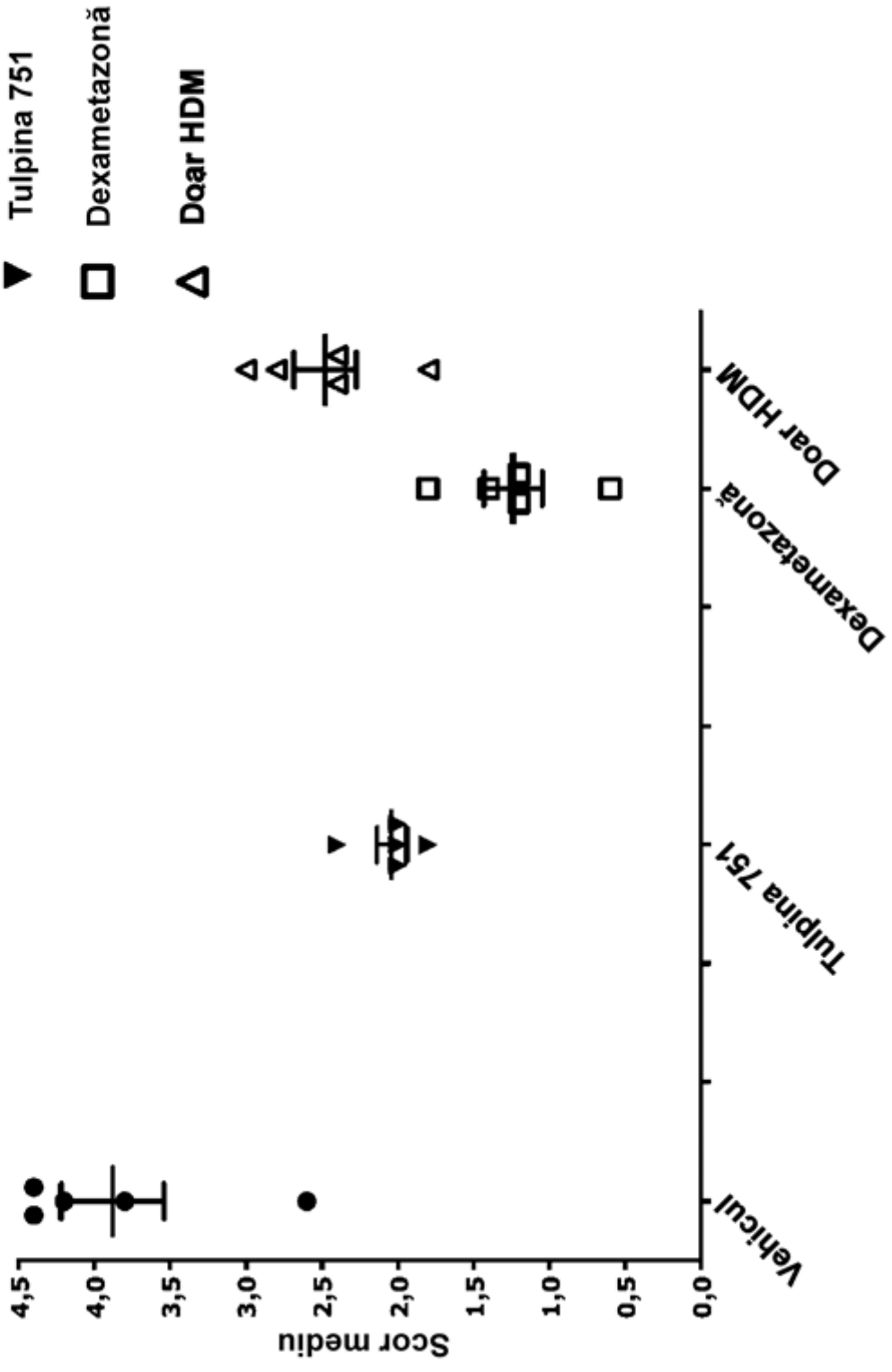


FIG. 33

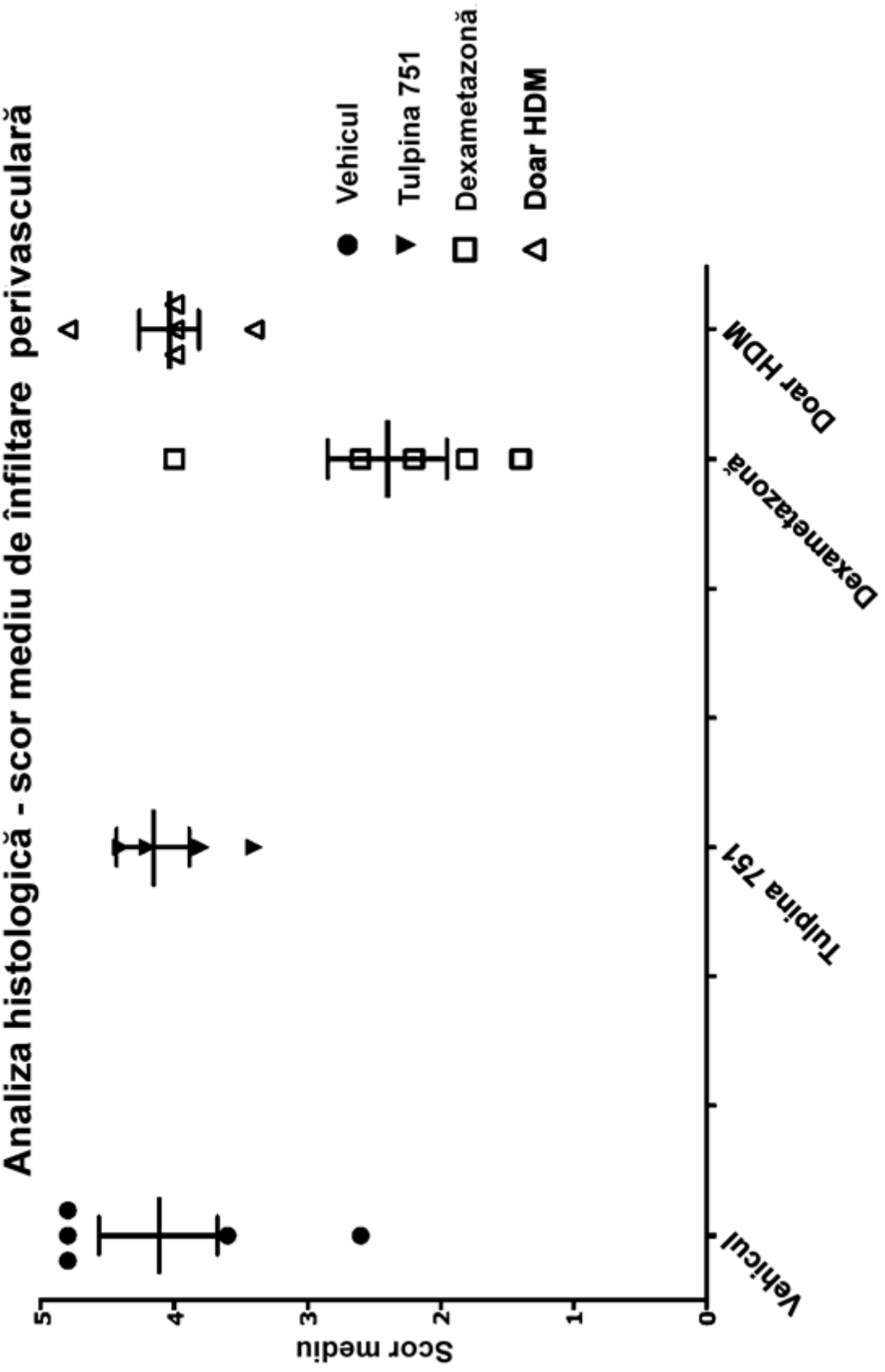

Analiza histologică - scor mediu de înfiltare perivasculară
Scor mediu
0
1
2
3
4
5
Vehicul
Tulpina 751
Dexametazonă
Doar HDM
Vehicul
Tulpina 751
Dexametazonă
Doar HDM

FIG. 34

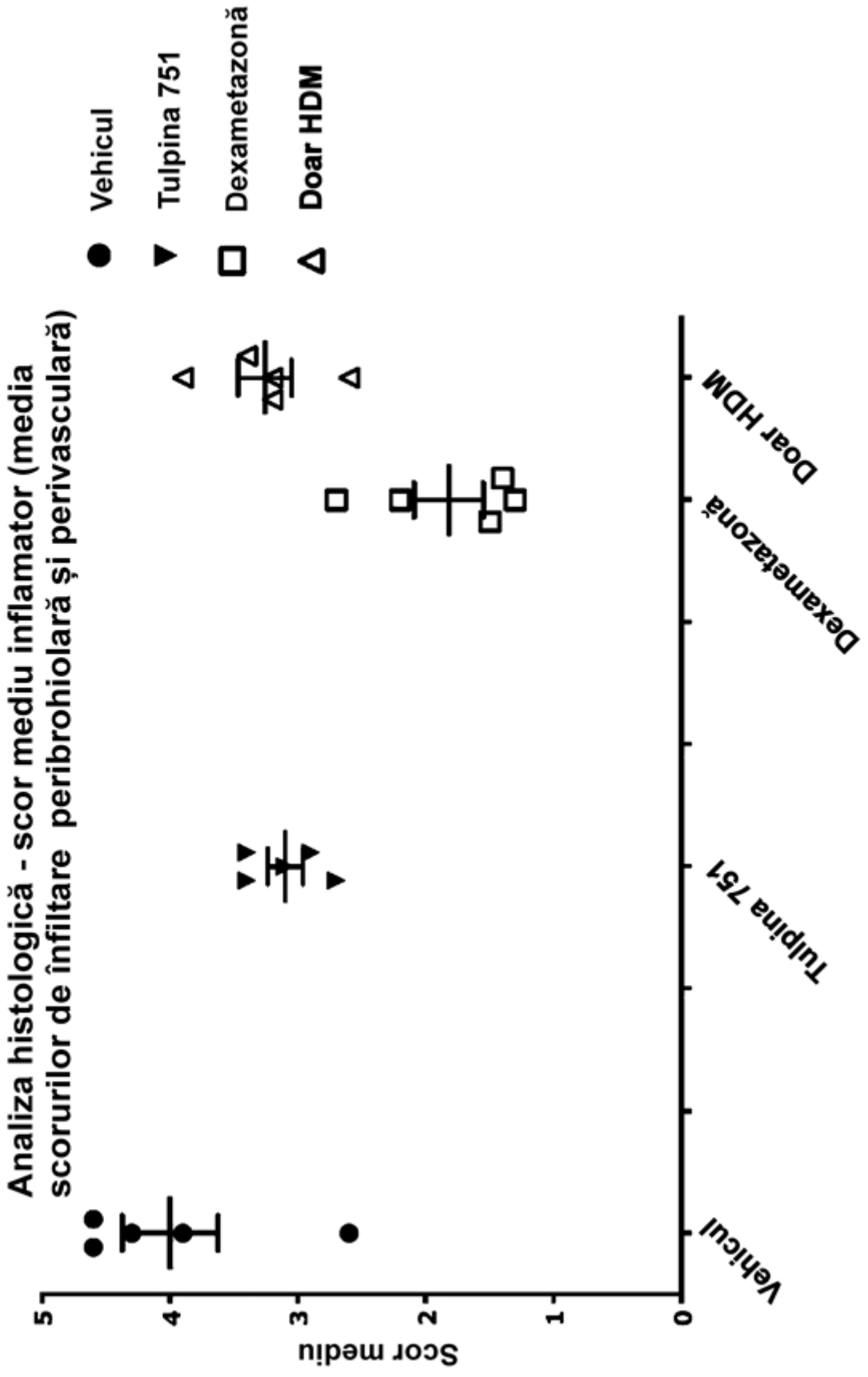

Analiza histologică - scor mediu inflamator (media scorurilor de infiltare peribrohiolară și perivasculară)
Vehicul
Tulpina 751
Dexametazonă
Doar HDM
Scor mediu
0
1
2
3
4
5
Vehicul
Tulpina 751
Dexametazonă
Doar HDM

FIG. 35

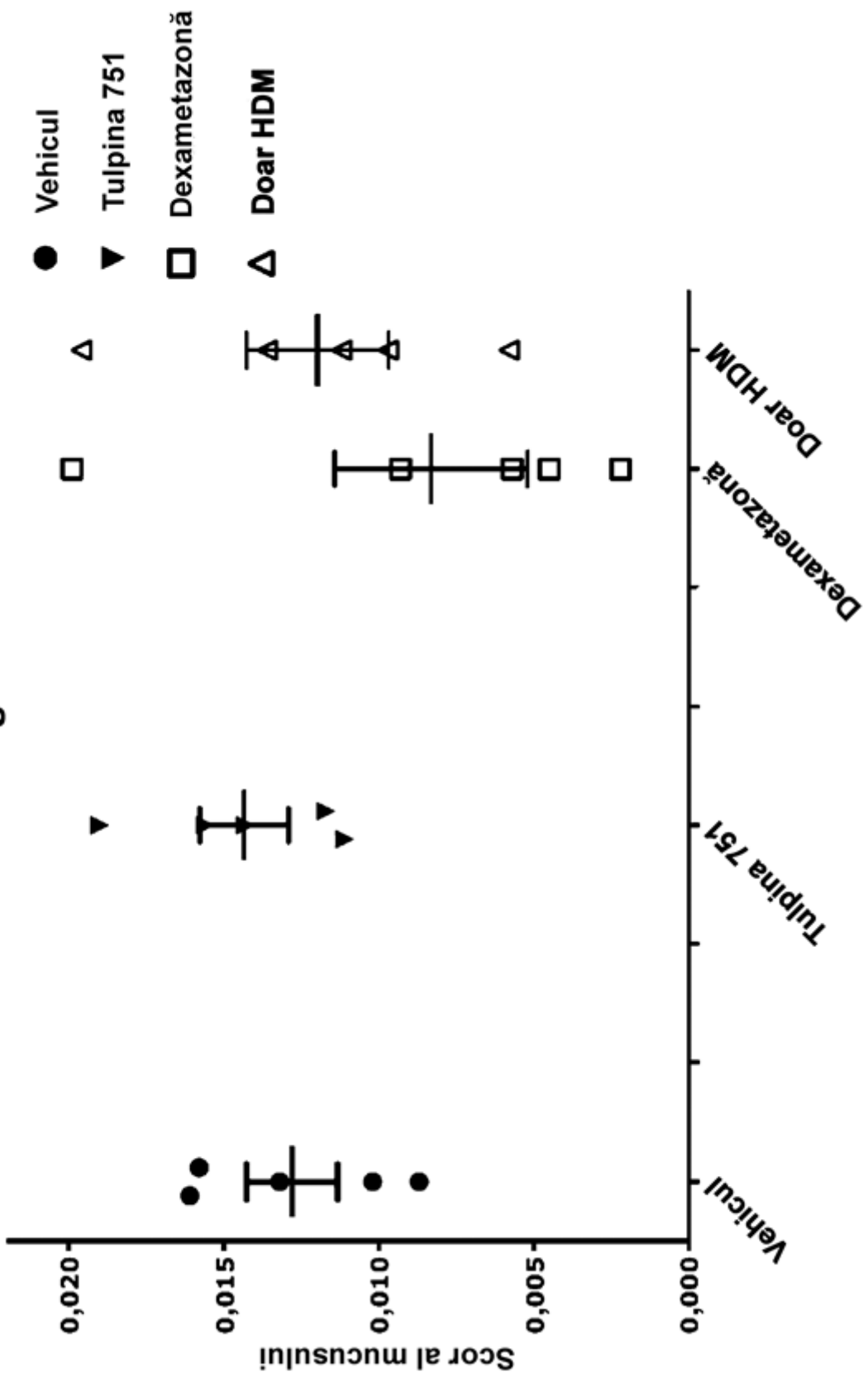

Analiza histologică - scorul mucusului
Vehicul
Tulpina 751
Dexametazonă
Doar HDM
Scor al mucusului
0,020
0,015
0,010
0,005
0,000
Vehicul
Tulpina 751
Dexametazonă
Doar HDM

FIG. 36

Nivelul IL-9 în țesutul pulmonar

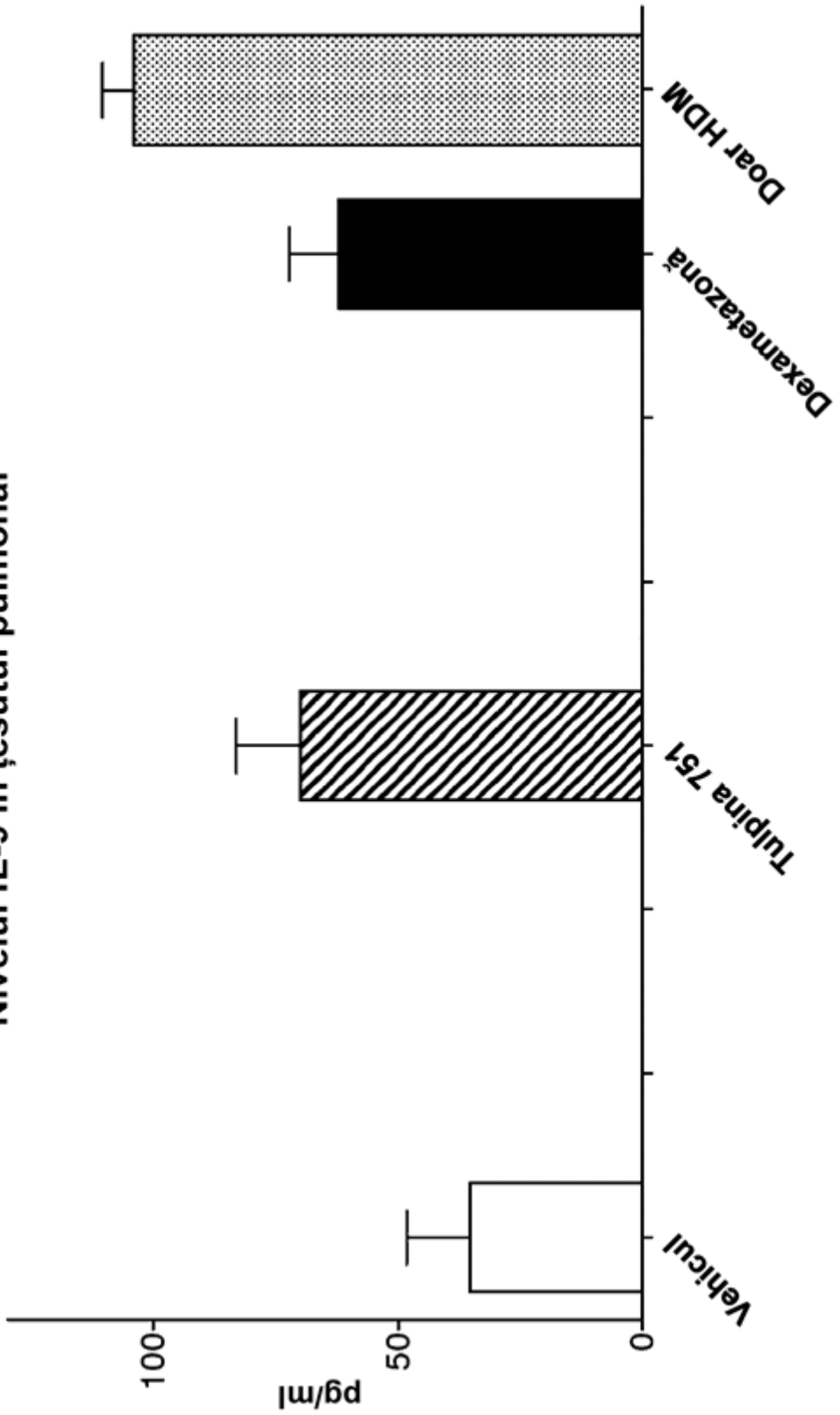


FIG. 37

Nivelul IL-1a în țesutul pulmonar

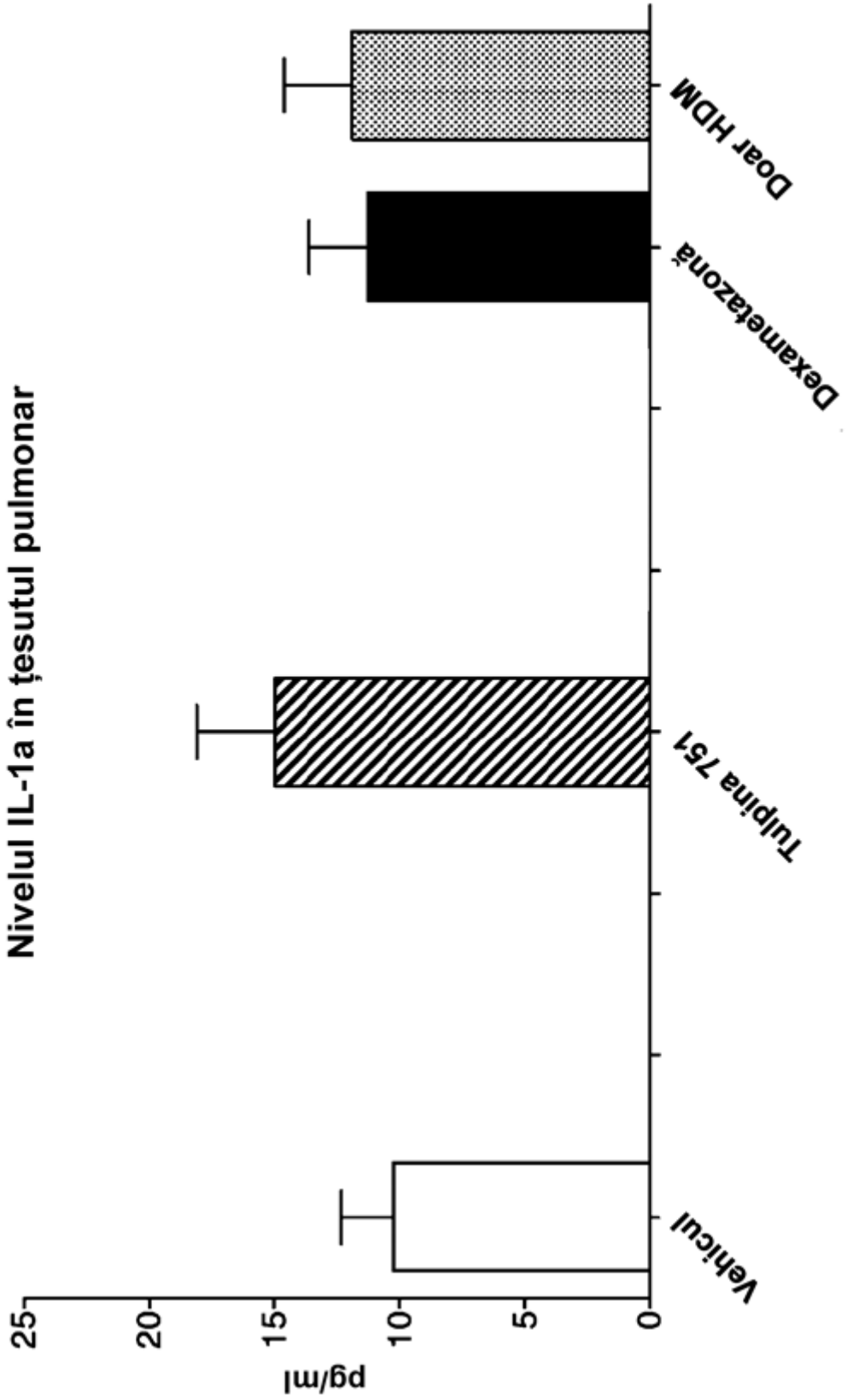


FIG. 38

Nivelul IFNg în țesutul pulmonar

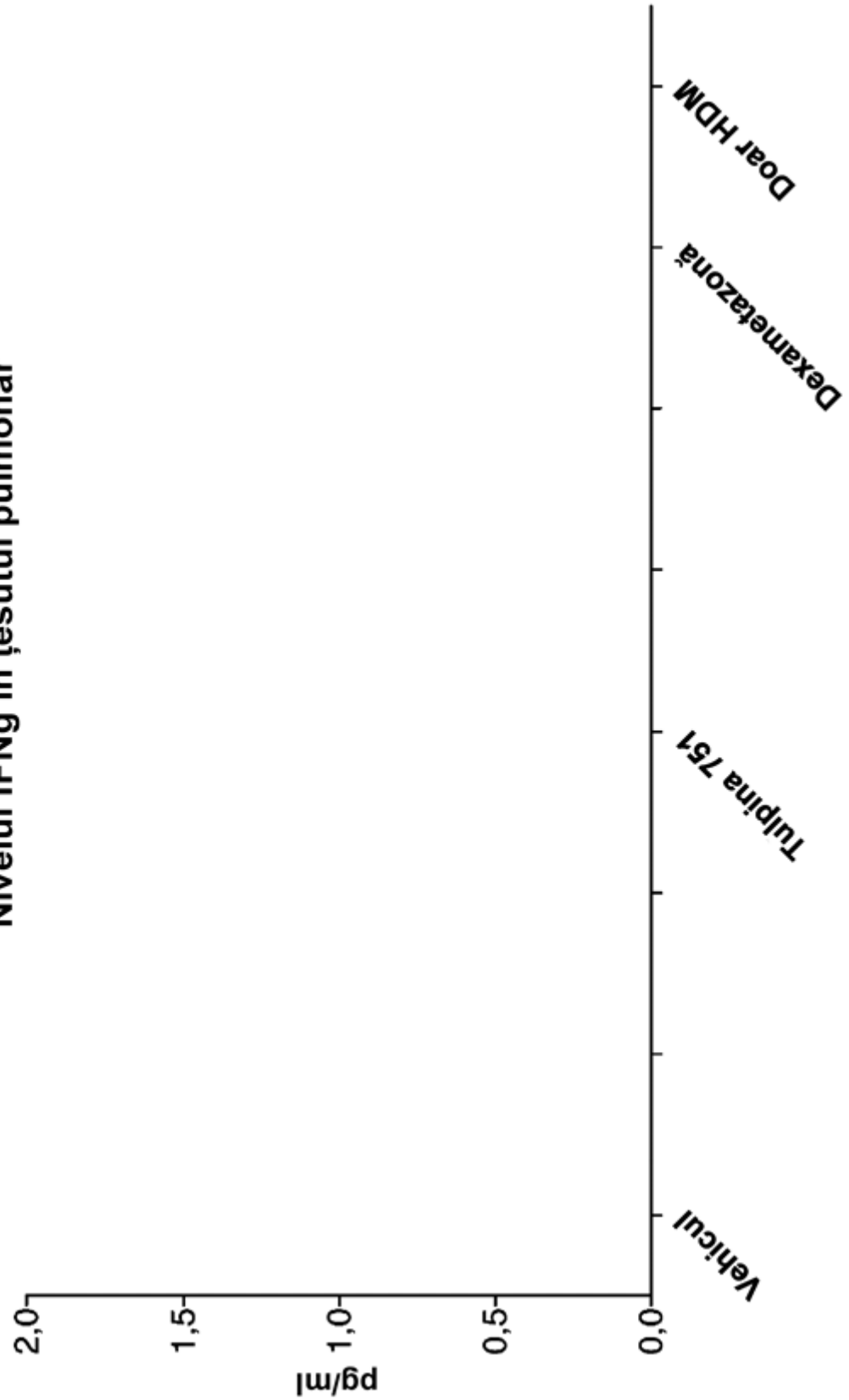


FIG. 39

Nivelul IL-17A în țesutul pulmonar

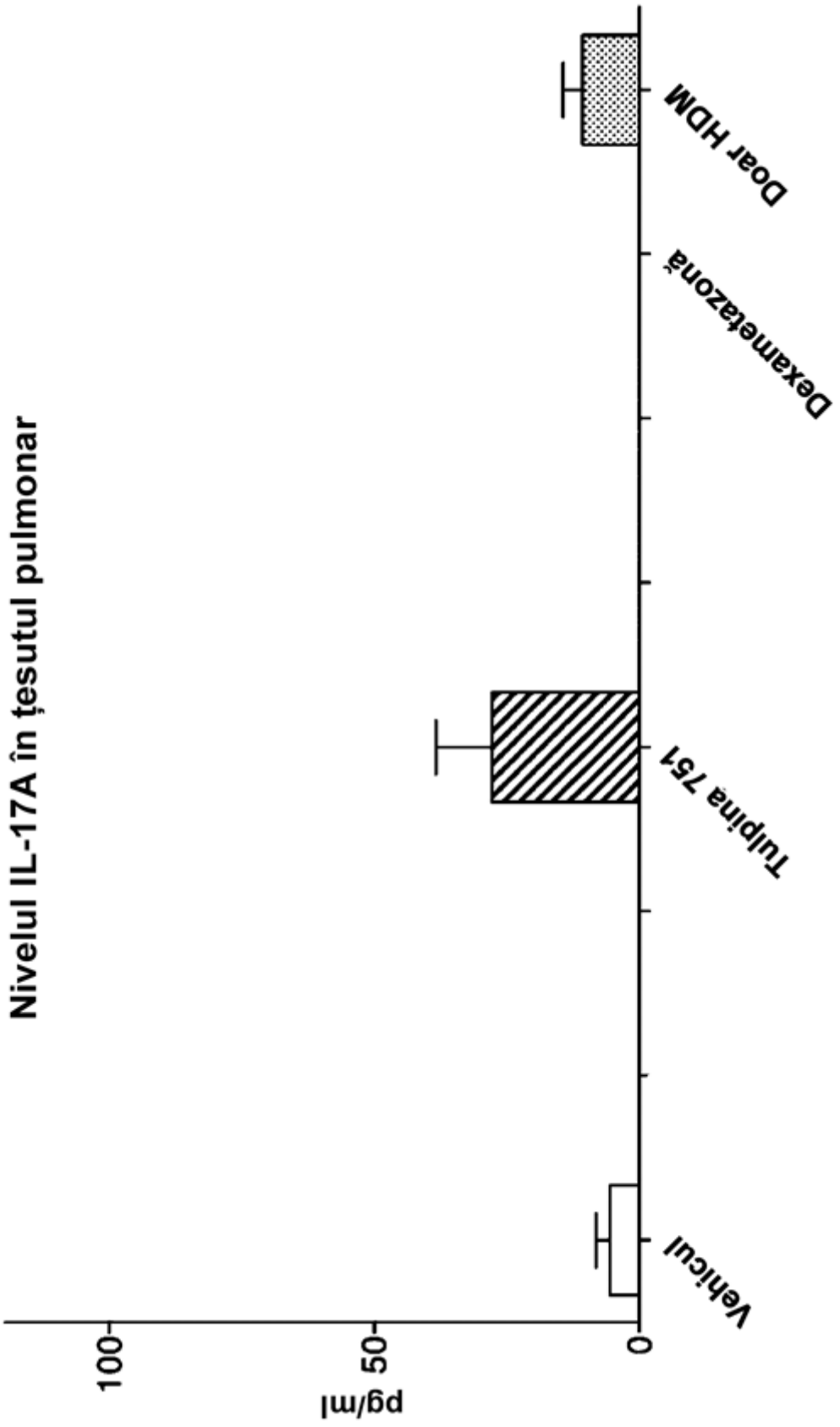


FIG. 40

Nivelul IL-4 în țesutul pulmonar

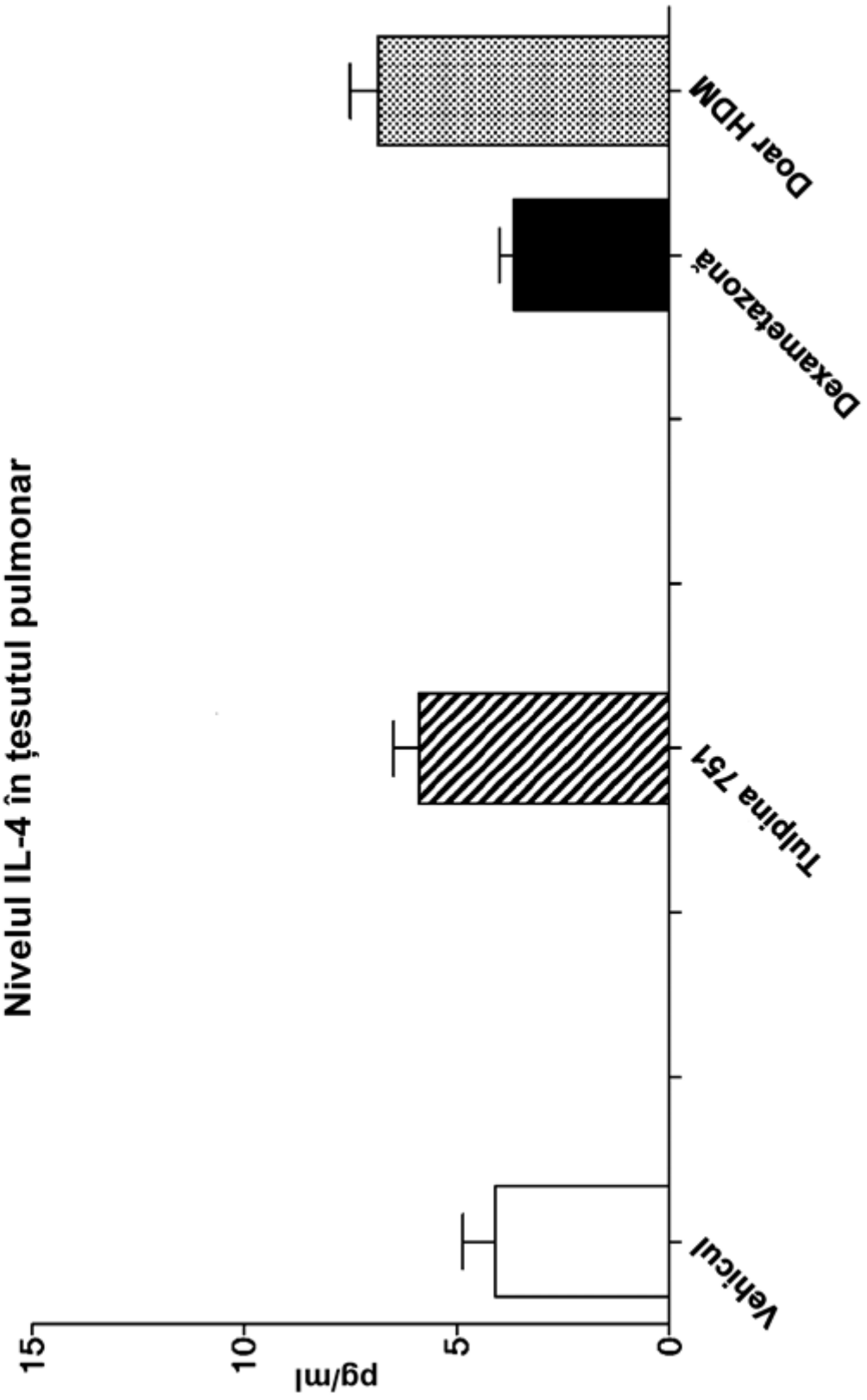


FIG. 41

Nivelul IL-5 în țesutul pulmonar

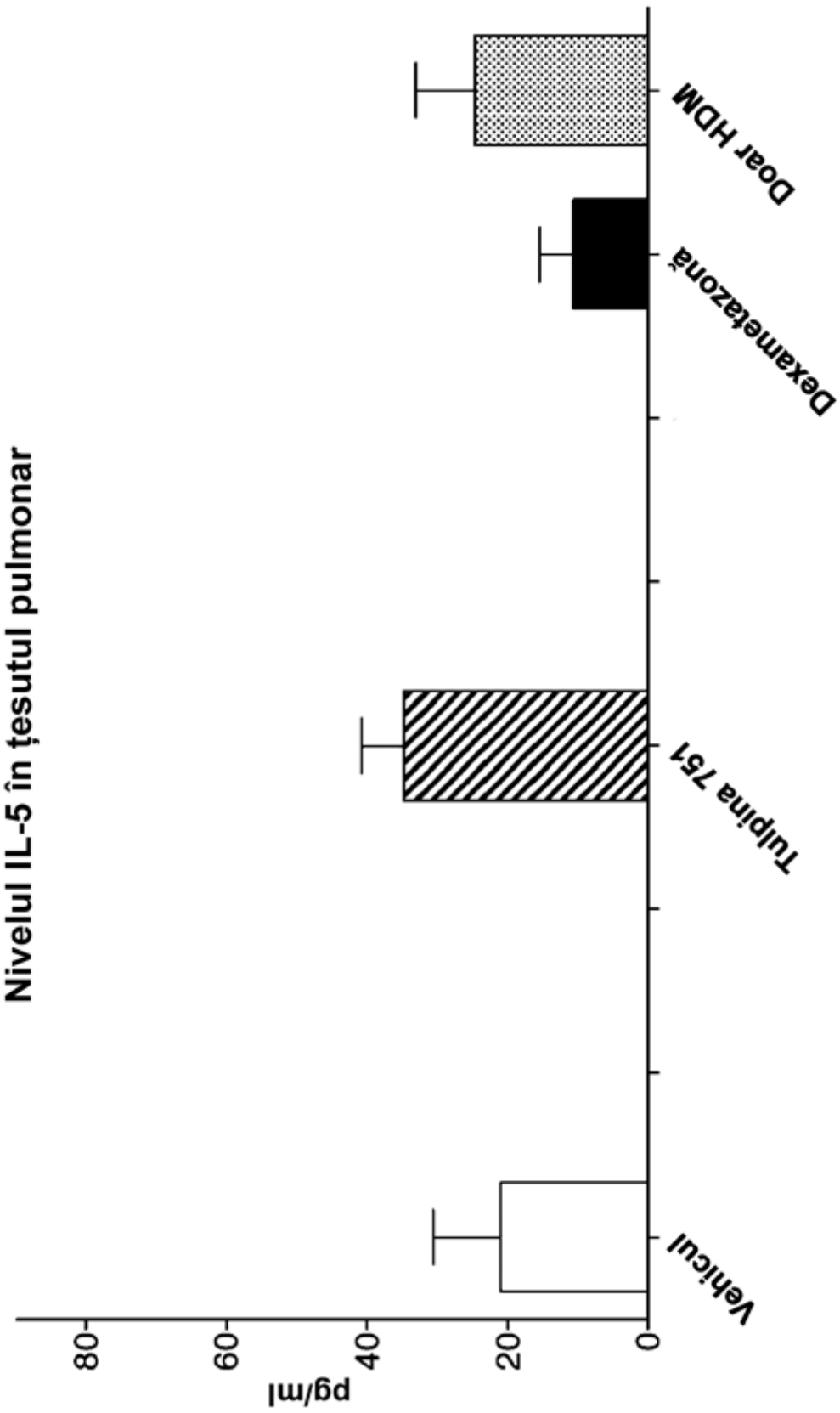


FIG. 42

Nivelul IL-1b în țesutul pulmonar

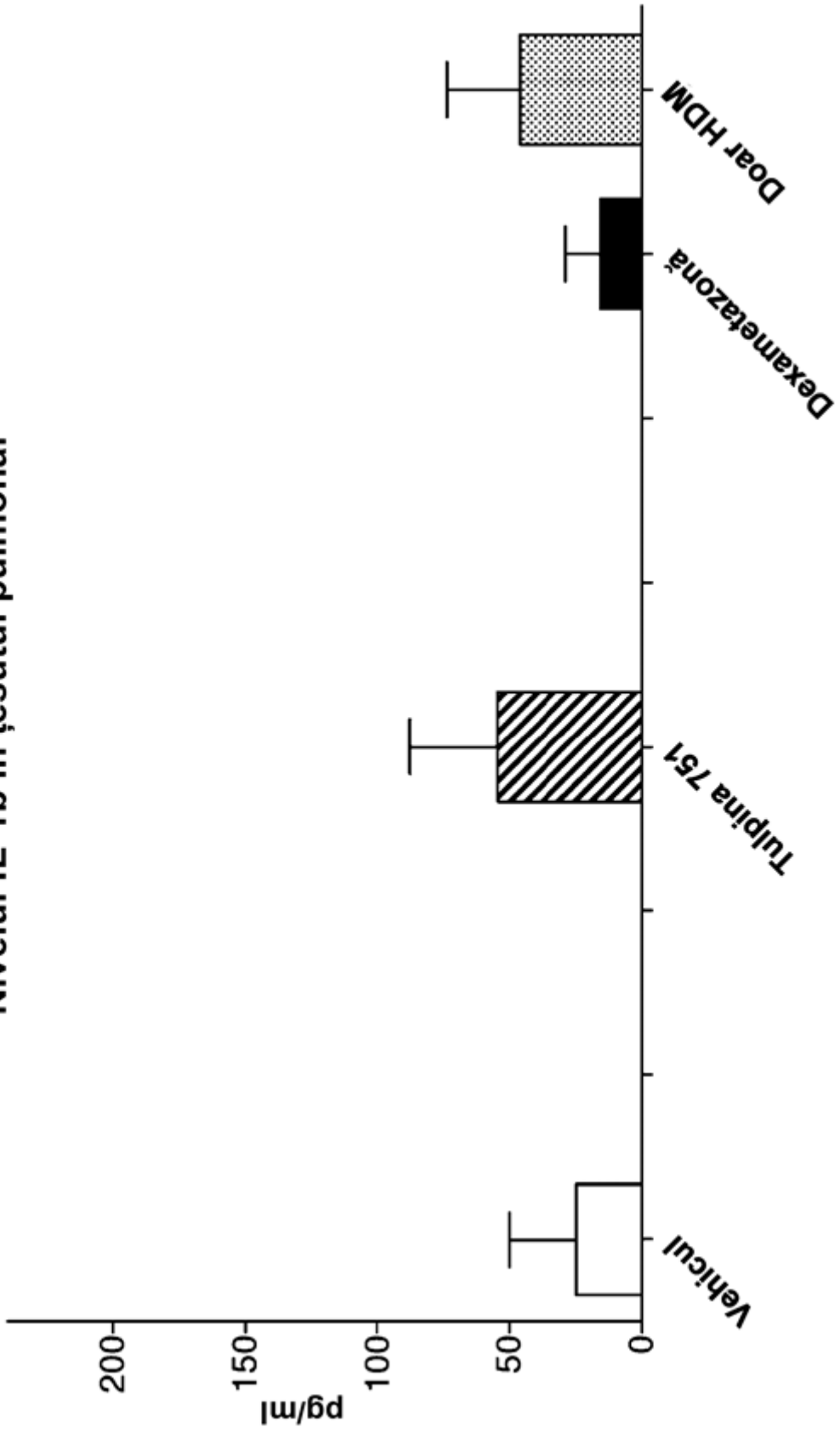


FIG. 43

Nivelul RANTES în țesutul pulmonar

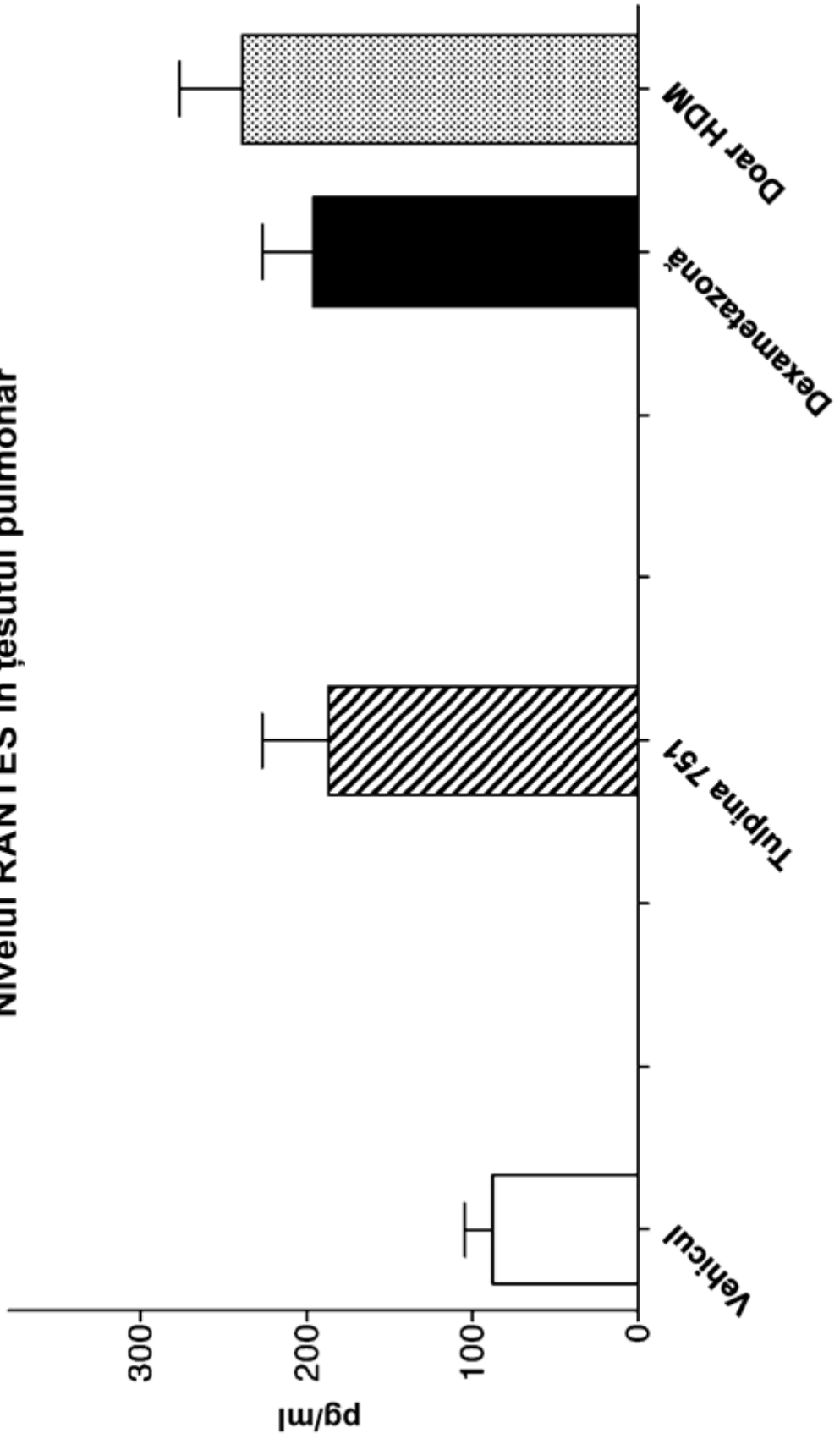


FIG. 44

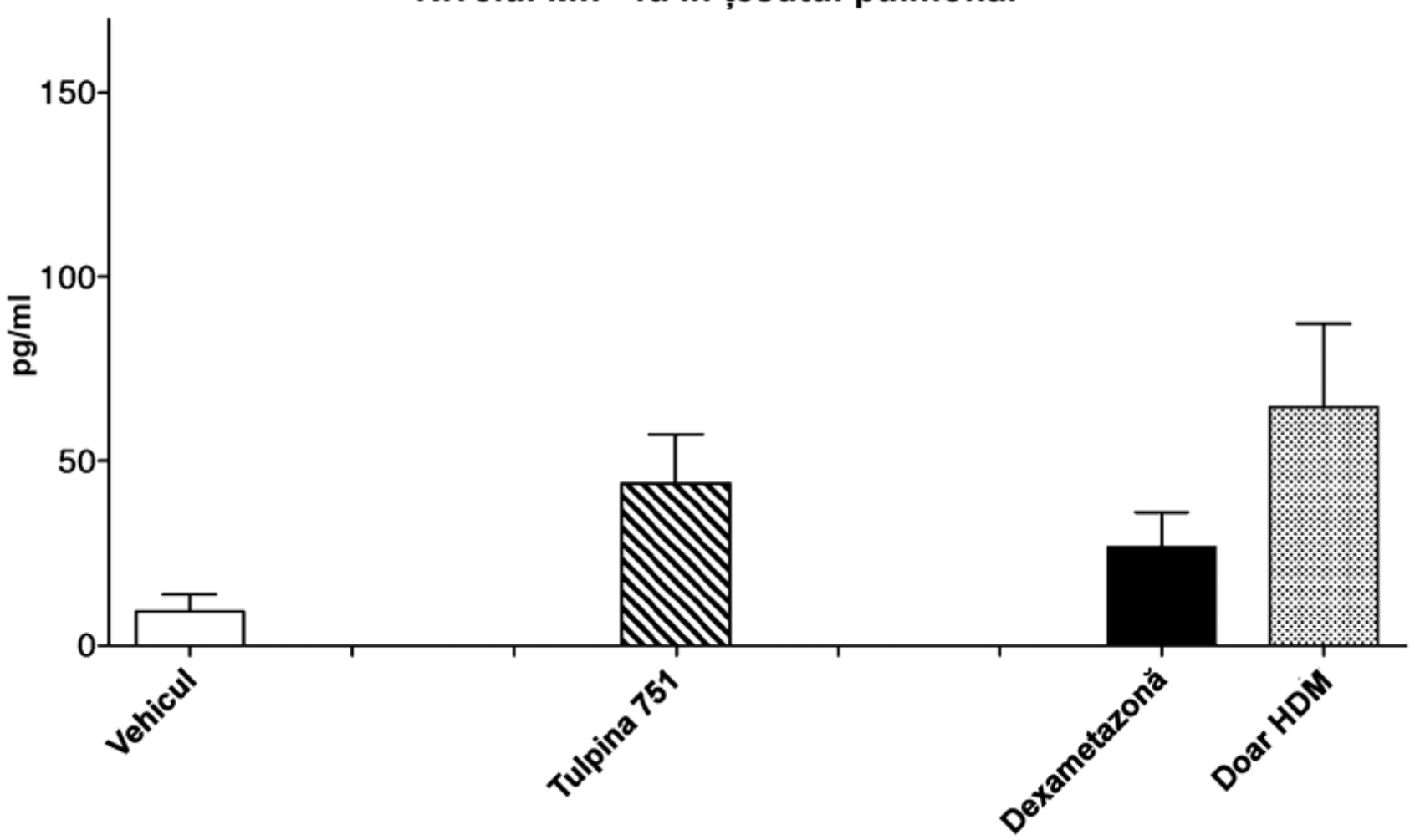


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FIG. 45

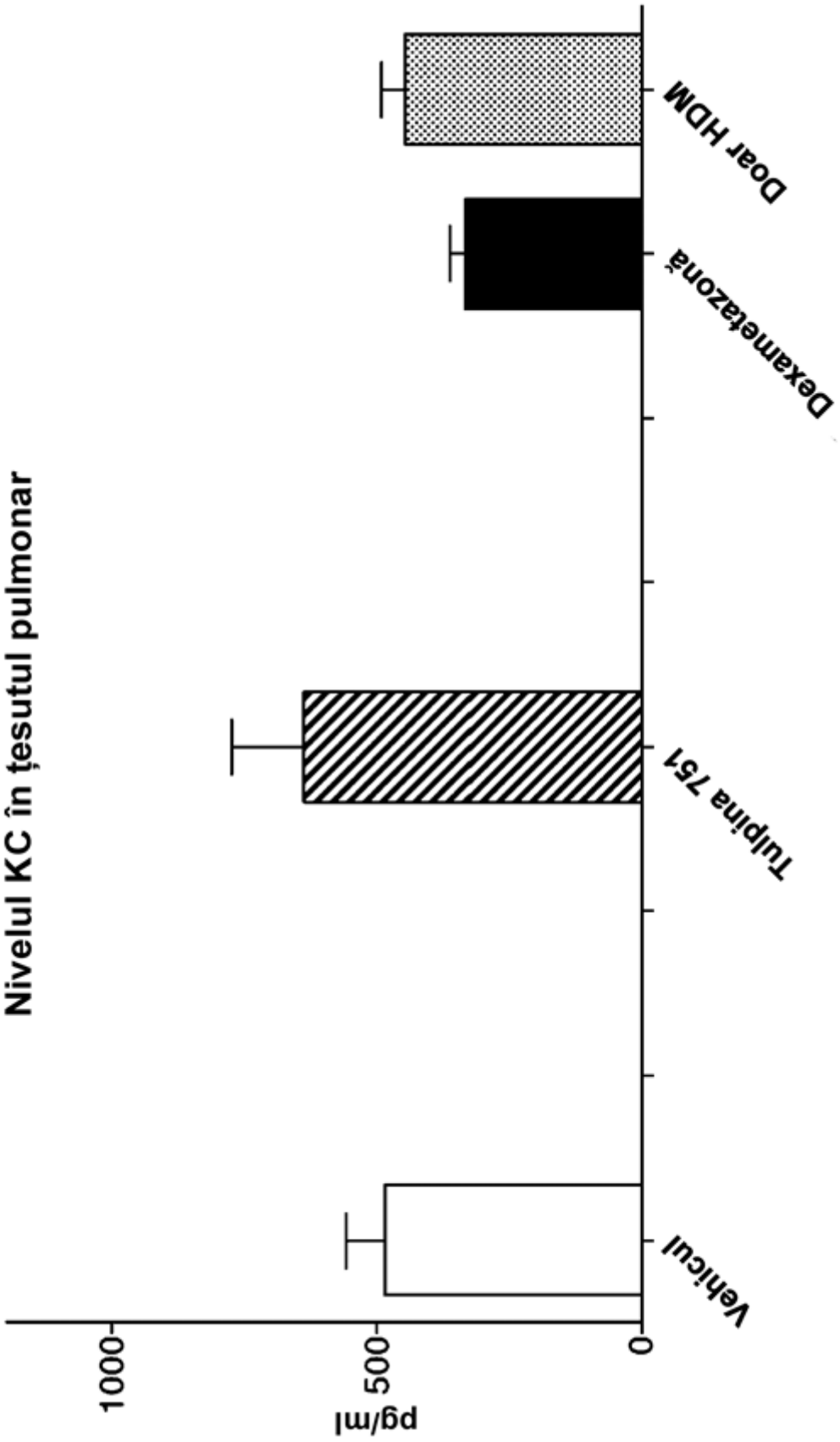
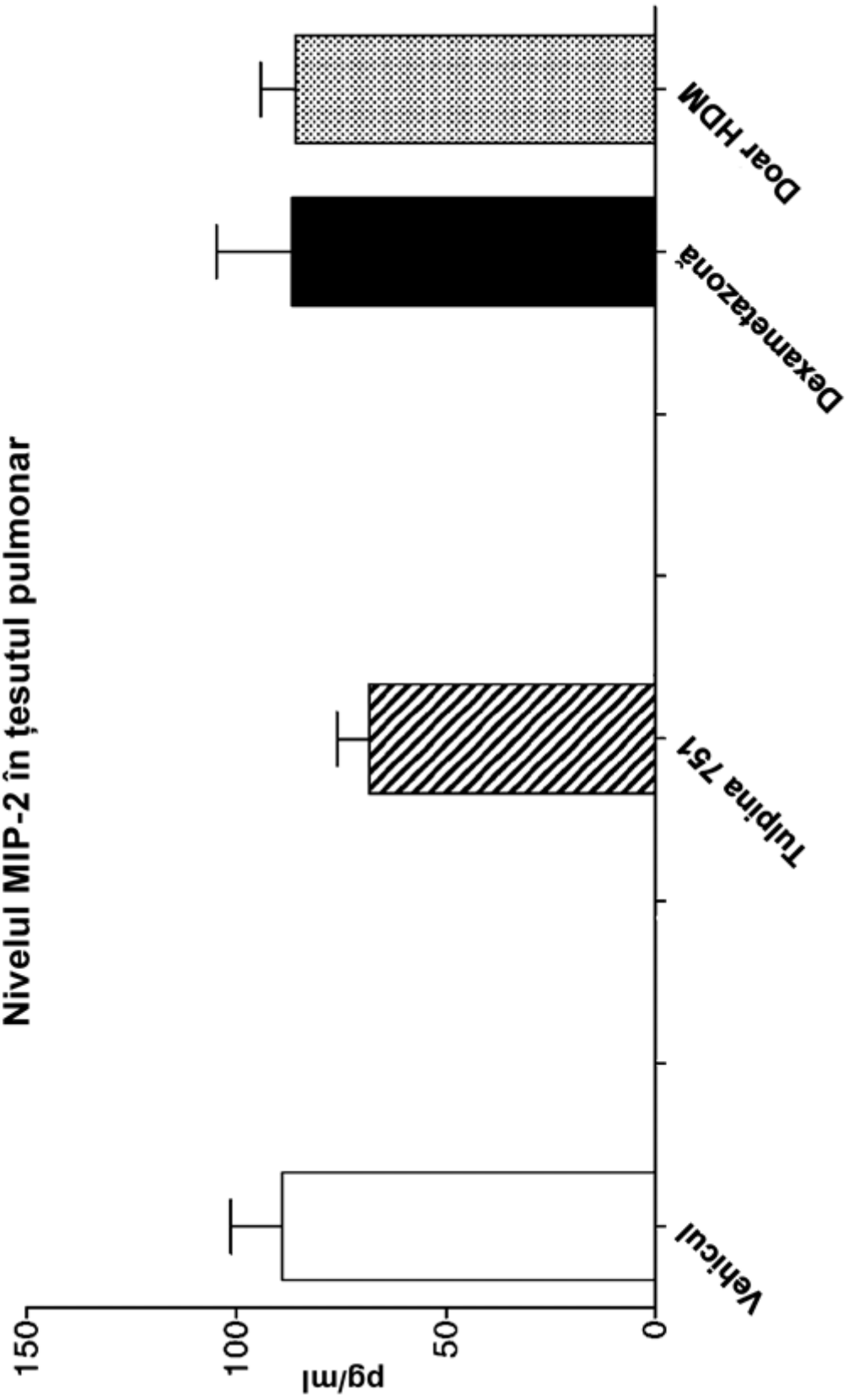

Nivelul KC în țesutul pulmonar
pg/ml
1000
500
0
Vehicul
Tulpina 751
Dexametazonă
Doar HDM

FIG. 46

Nivelul MIP-2 în țesutul pulmonar



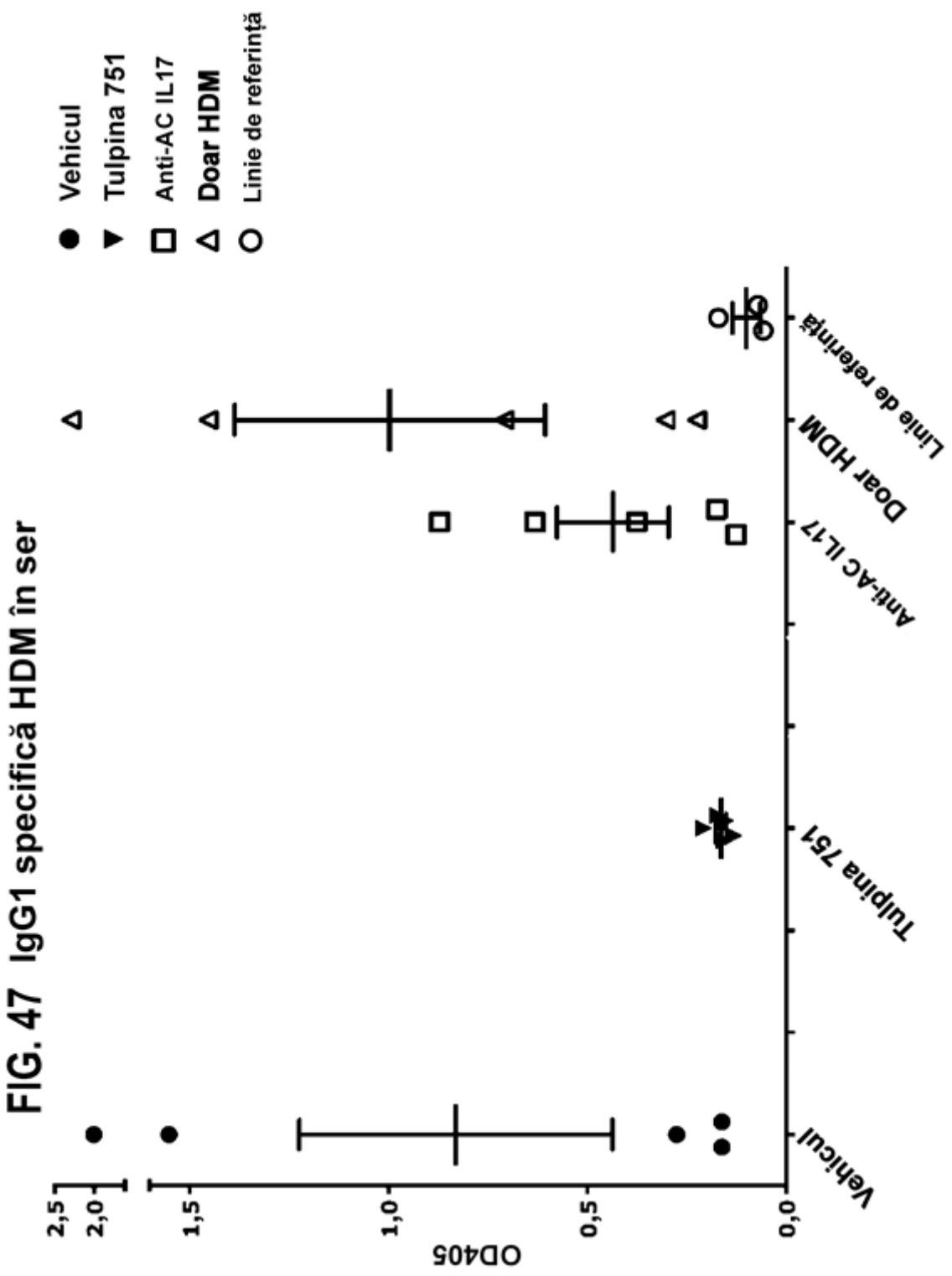


FIG. 47 IgG1 specifică HDM în ser

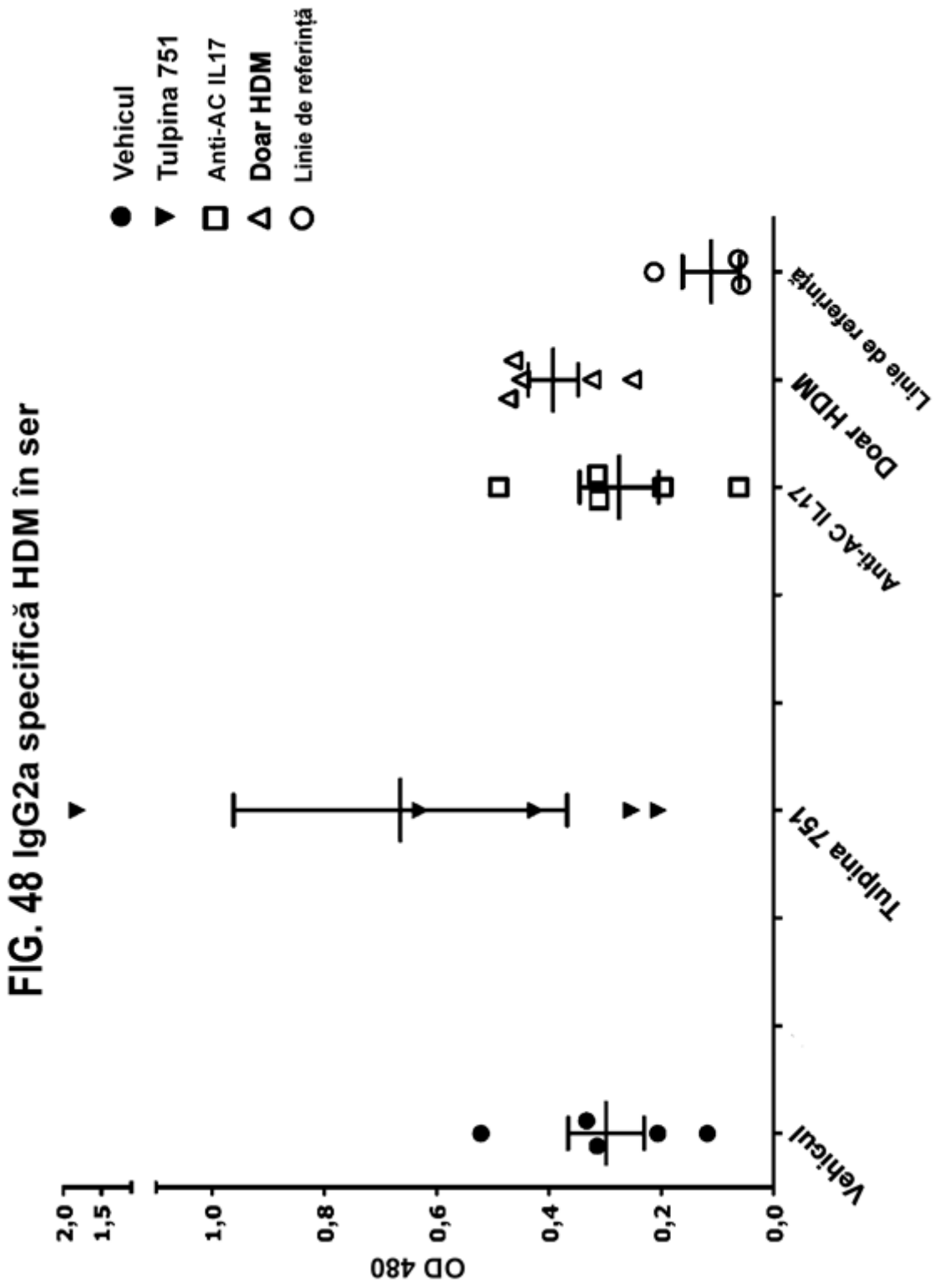


FIG. 48 IgG2a specifică HDM în ser

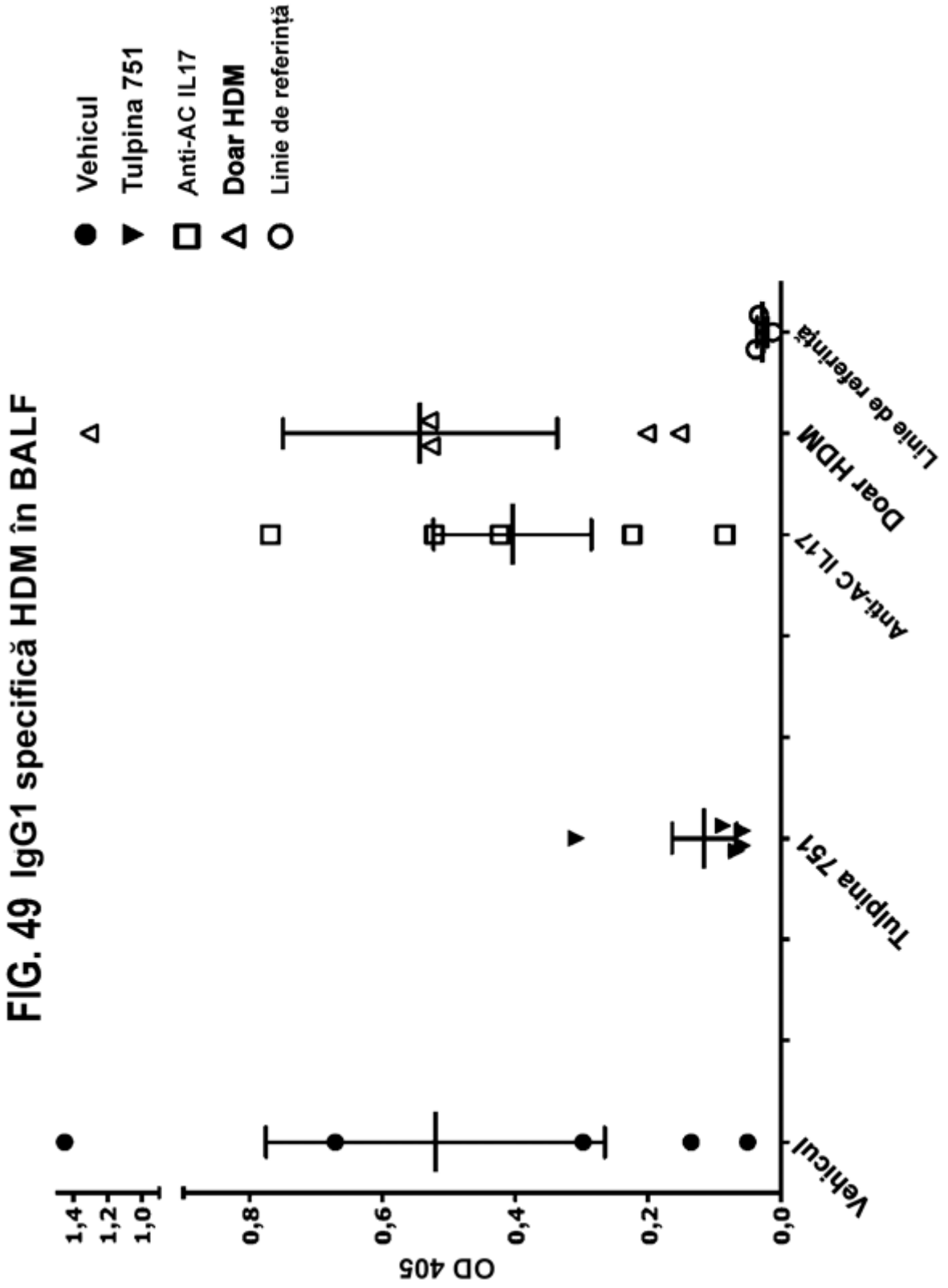


FIG. 49 IgG1 specifică HDM în BALF

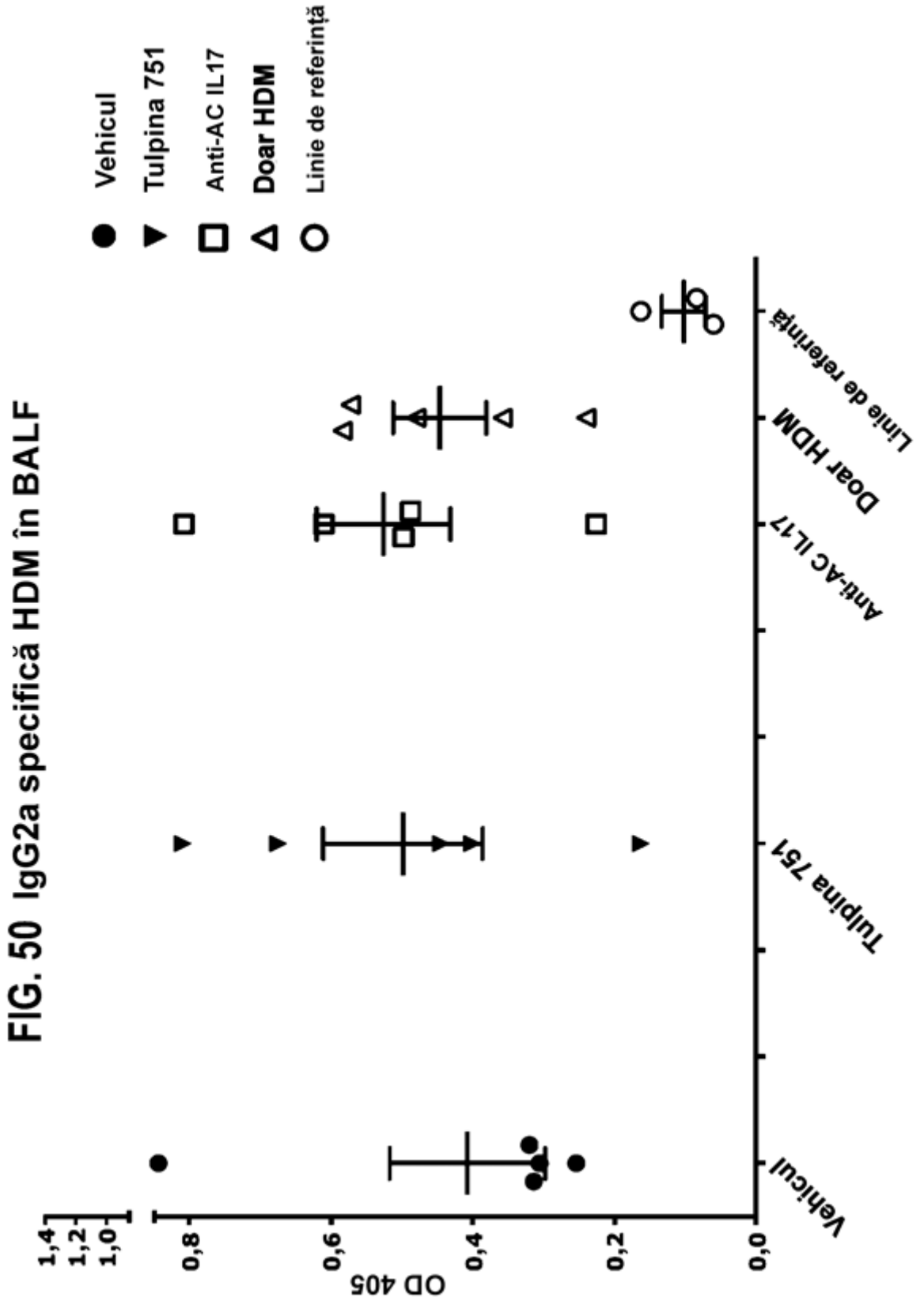


FIG. 50 IgG2a specifică HDM în BALF

FIG. 51 Analiza histologică - scor mediu de înfiltrare peribronhiolară

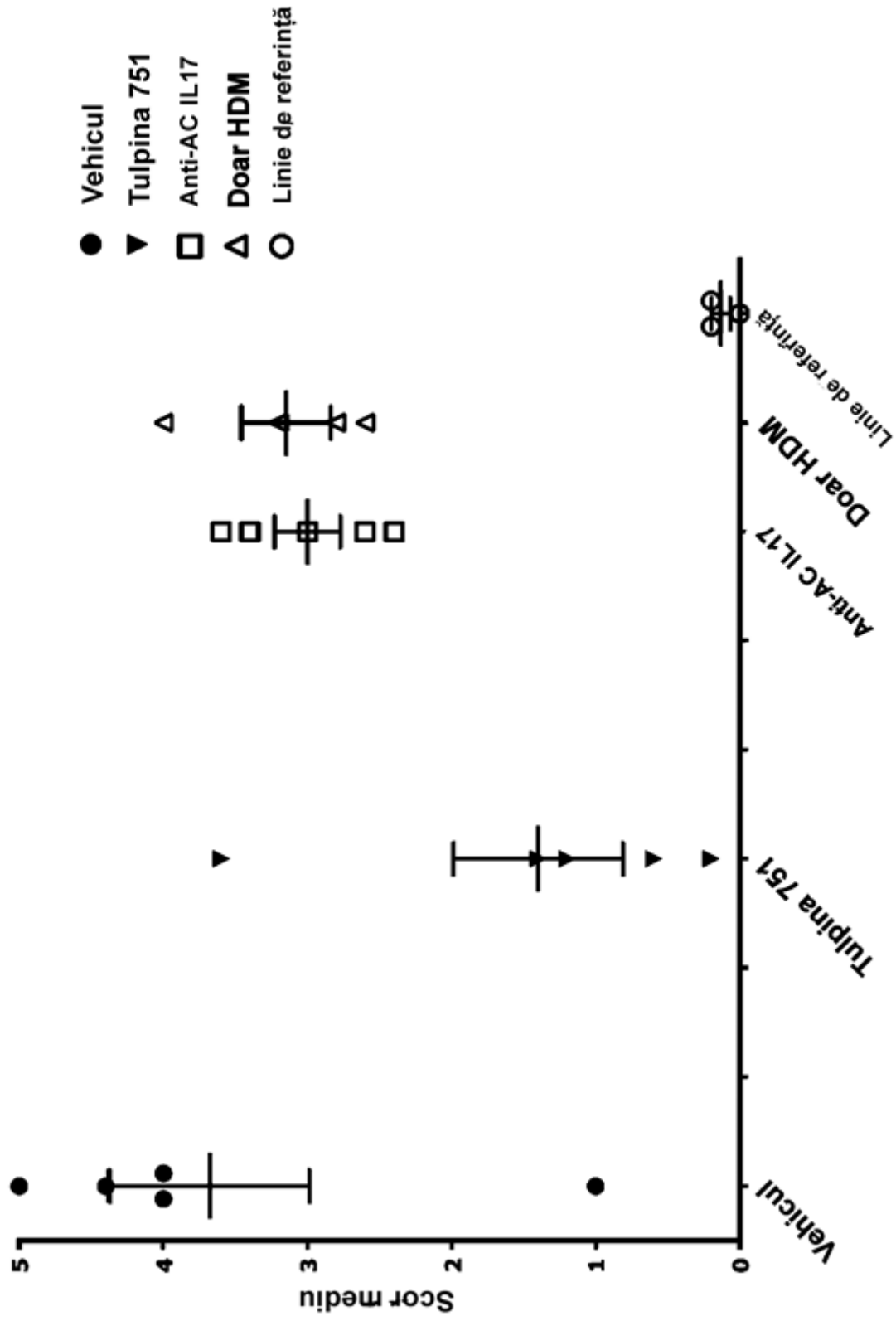


FIG. 52 Analiza histologică - scor mediu de înfiltrare perivasculară

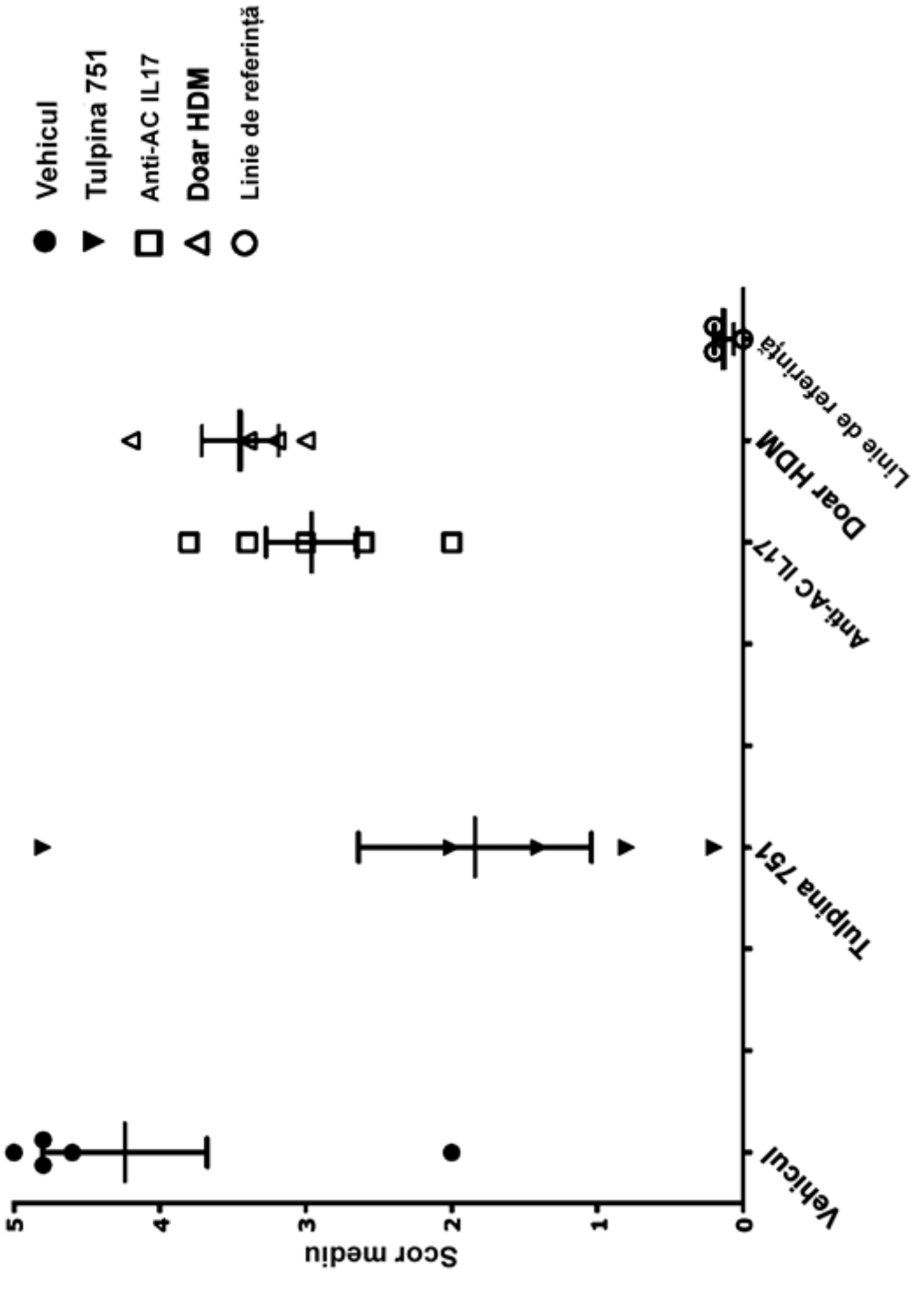


FIG. 53 Analiza histologică - scor mediu inflamator (media scorurilor de înfiltrare peribronhiolară și perivasculară)

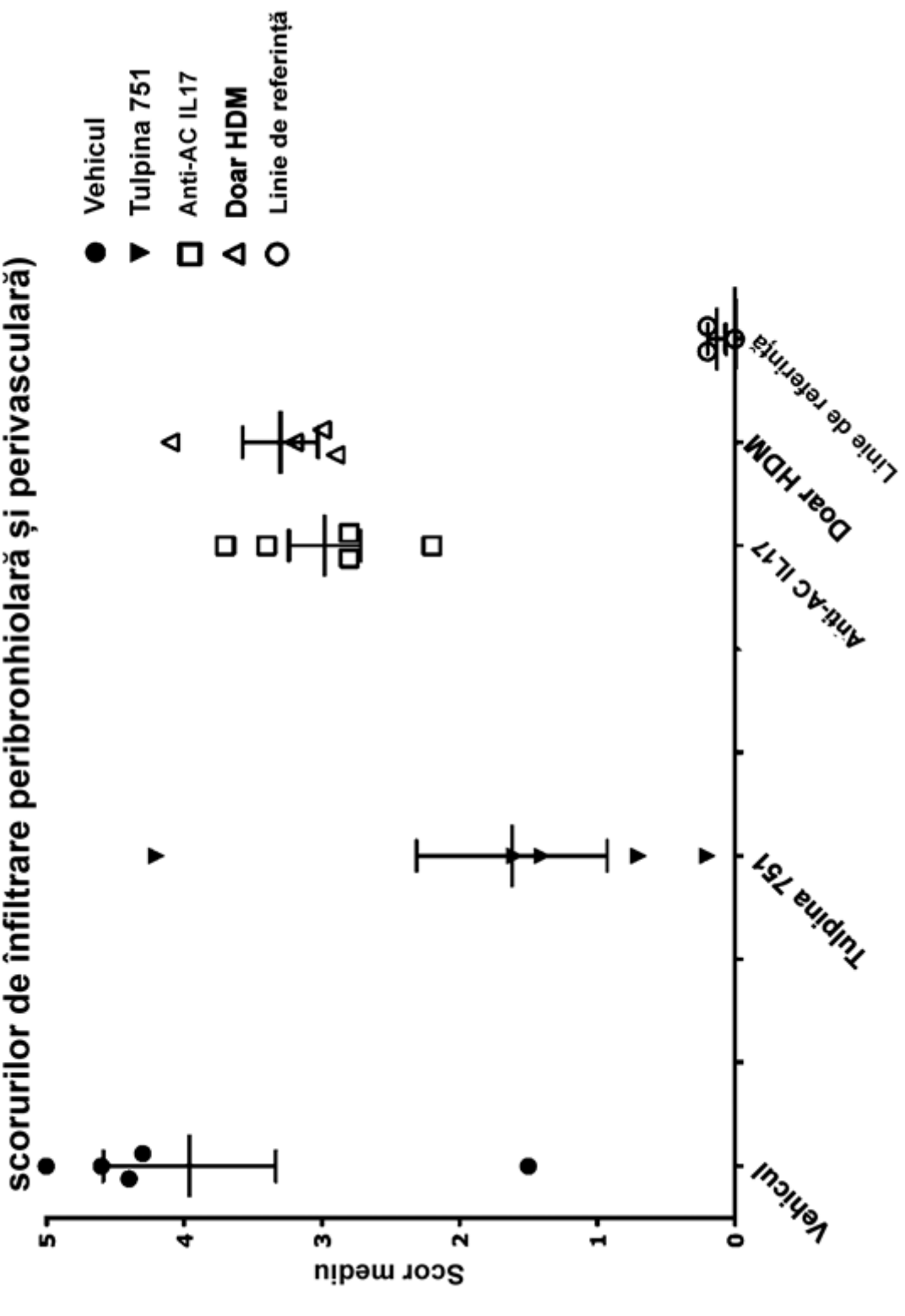


FIG. 54

Nivelul TNFa în țesutul pulmonar

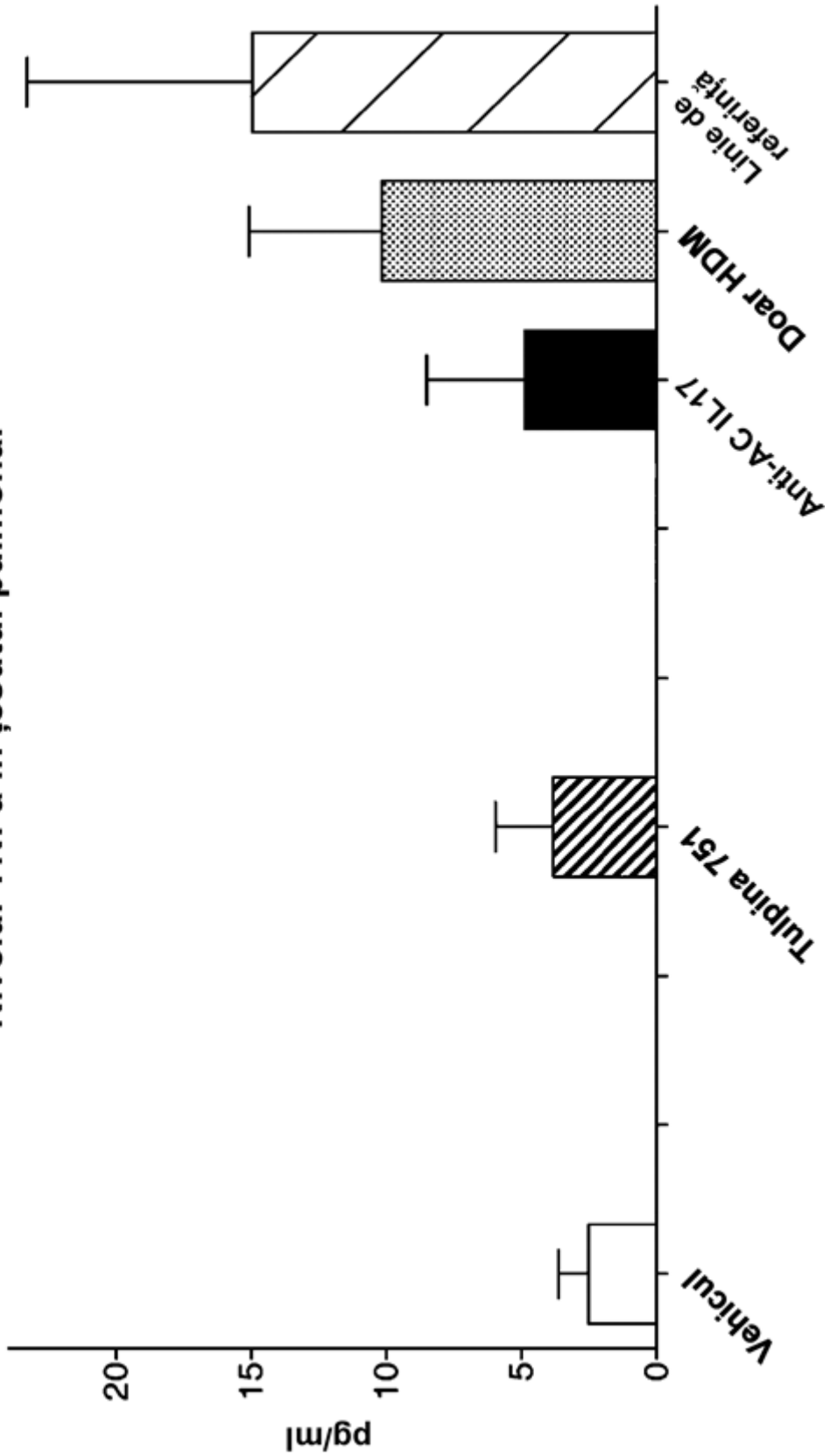


FIG. 55

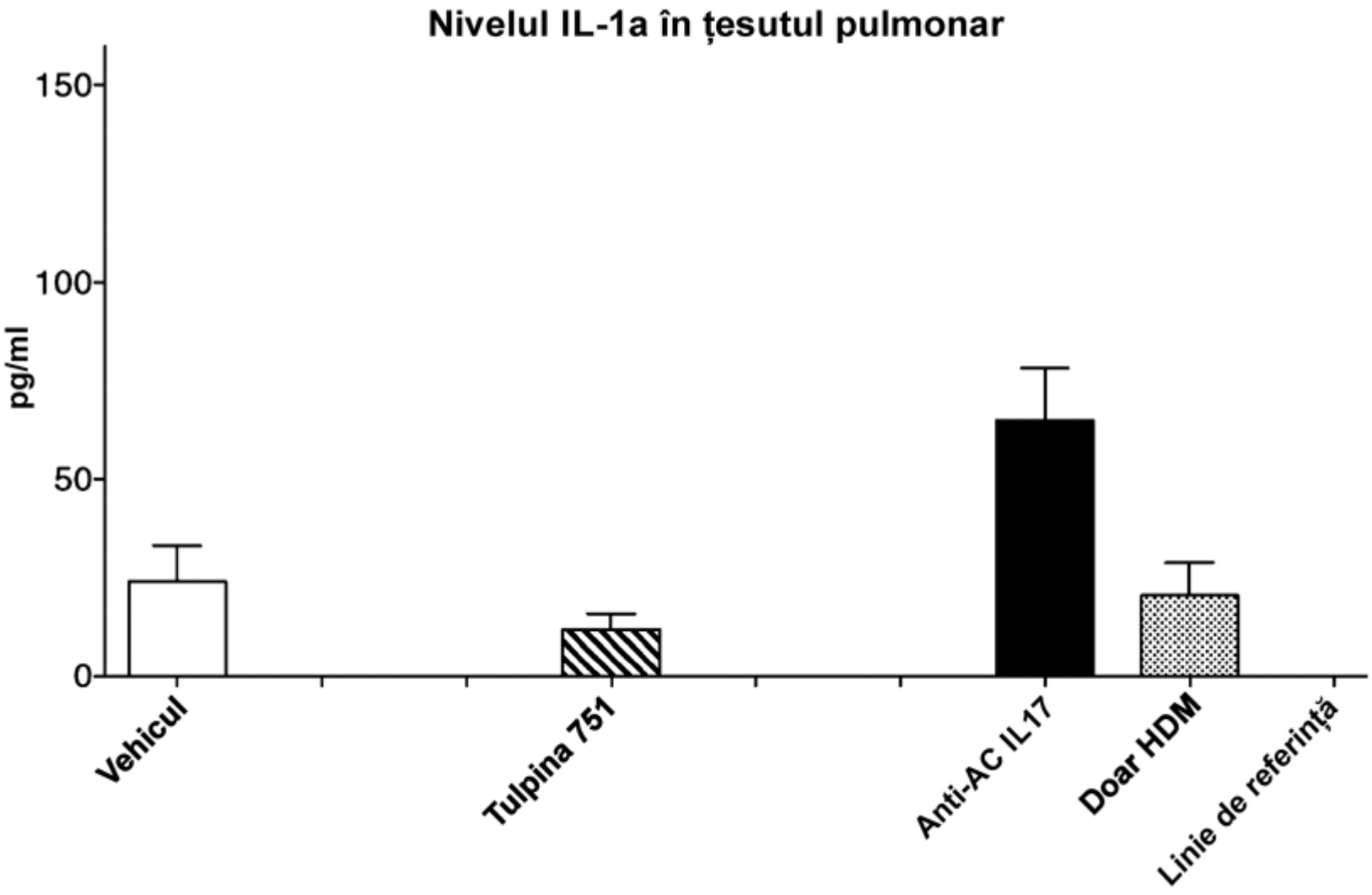


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FIG. 56

Nivelul IFNg în țesutul pulmonar

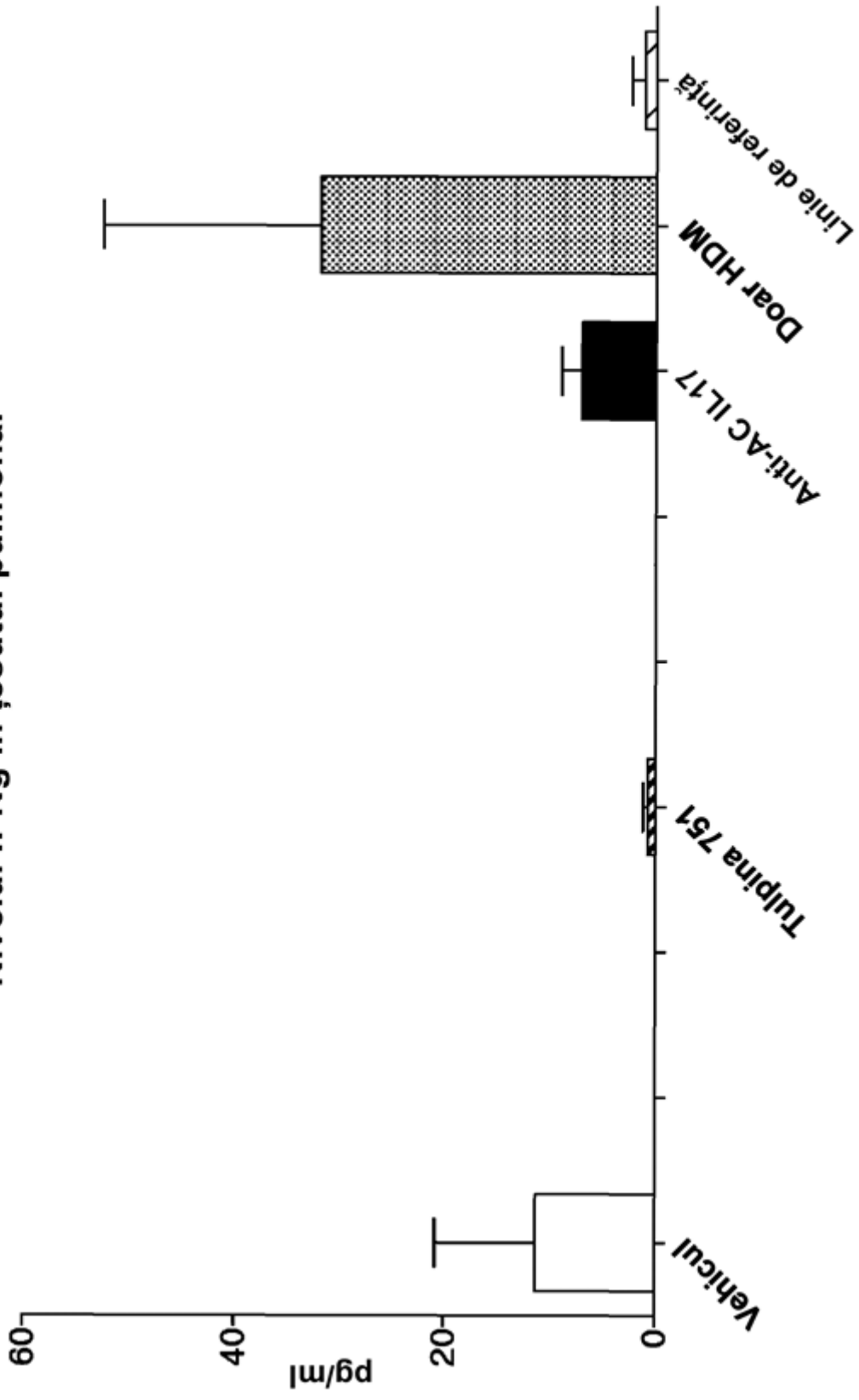


FIG. 57

Nivelul IL-17F în țesutul pulmonar

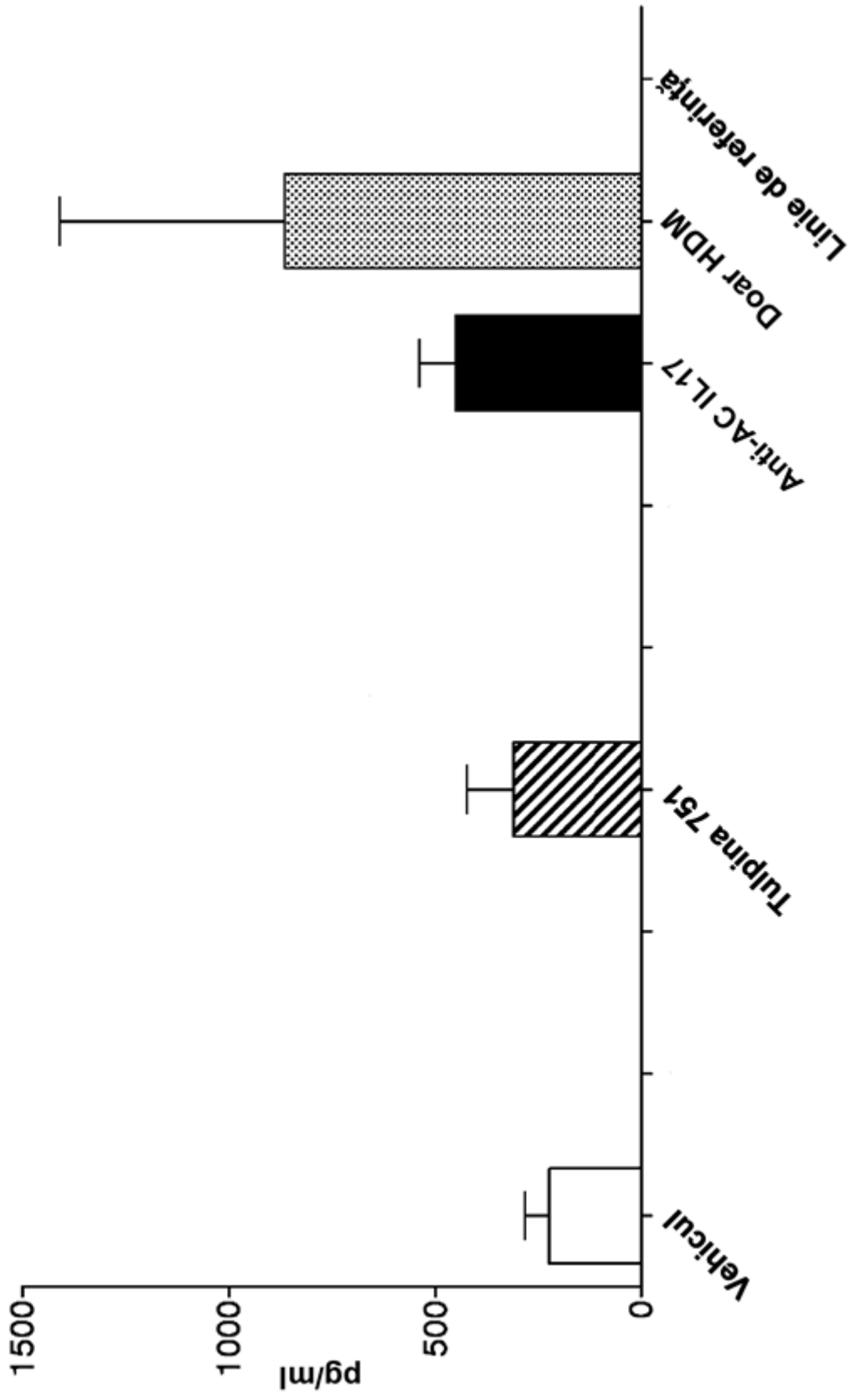


FIG. 58

Nivelul IL-1b în țesutul pulmonar

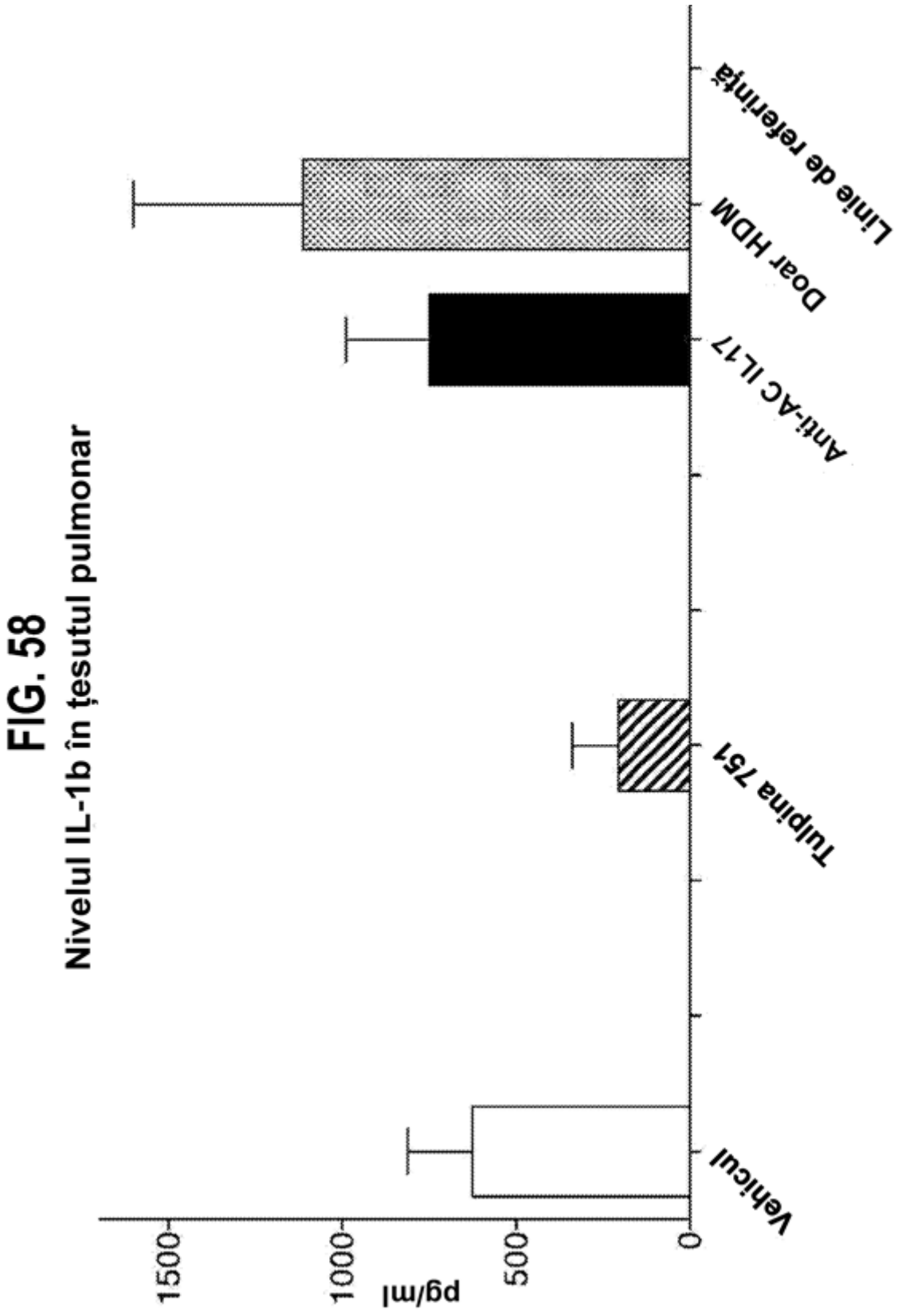
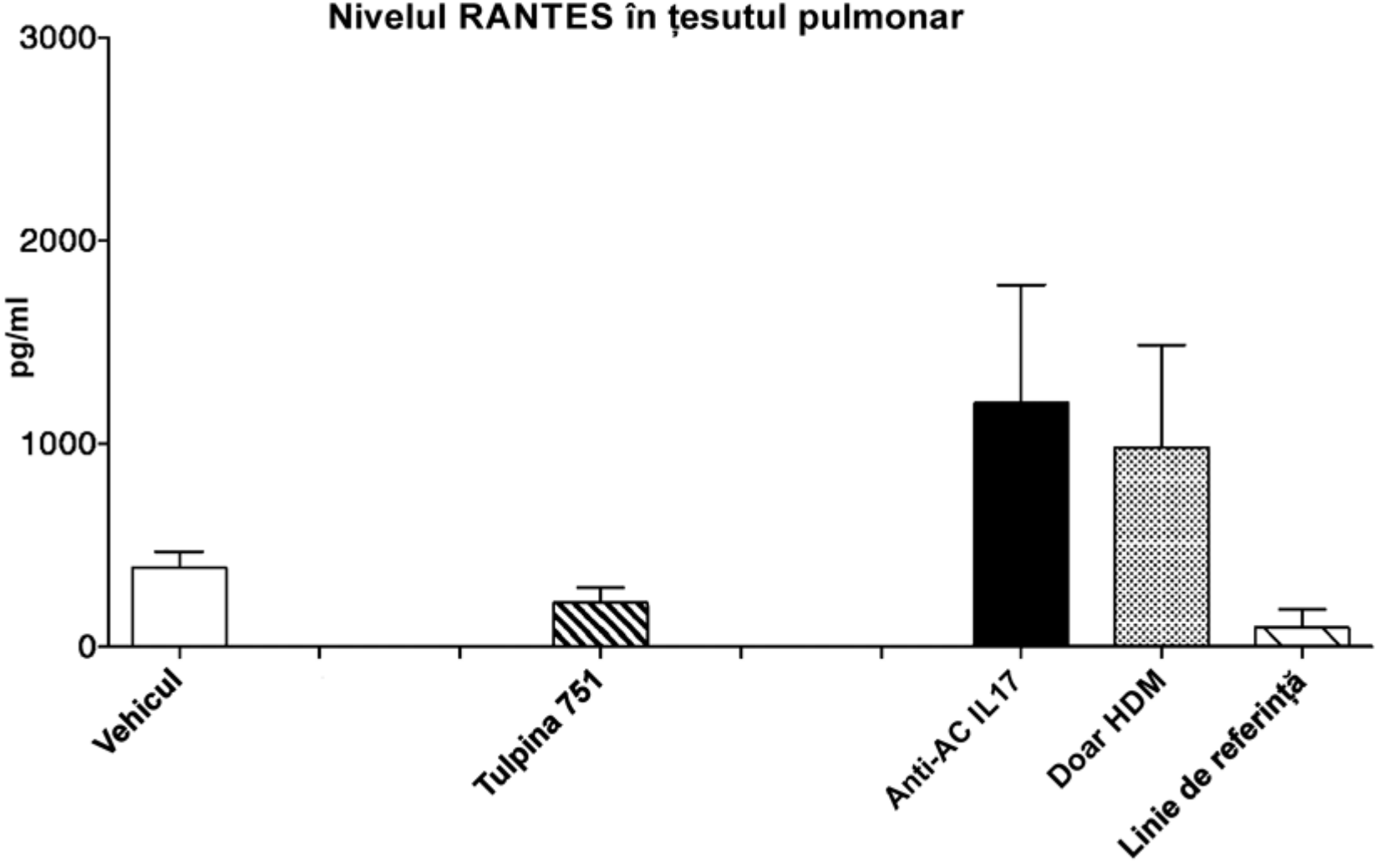
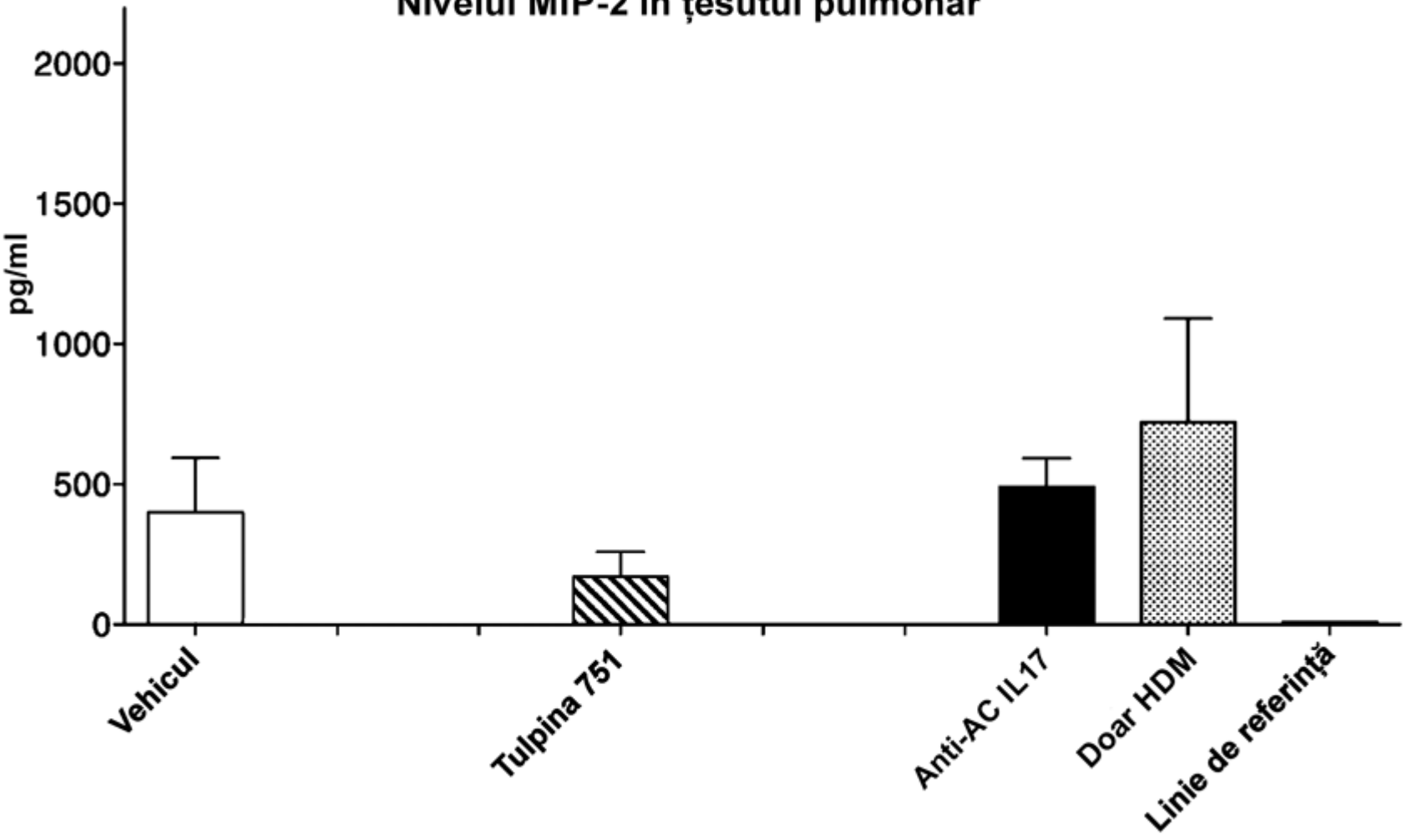


FIG. 59



e 2018 0809

FIG. 60



e 2018 0809

FIG. 61

Nivelul KC în țesutul pulmonar

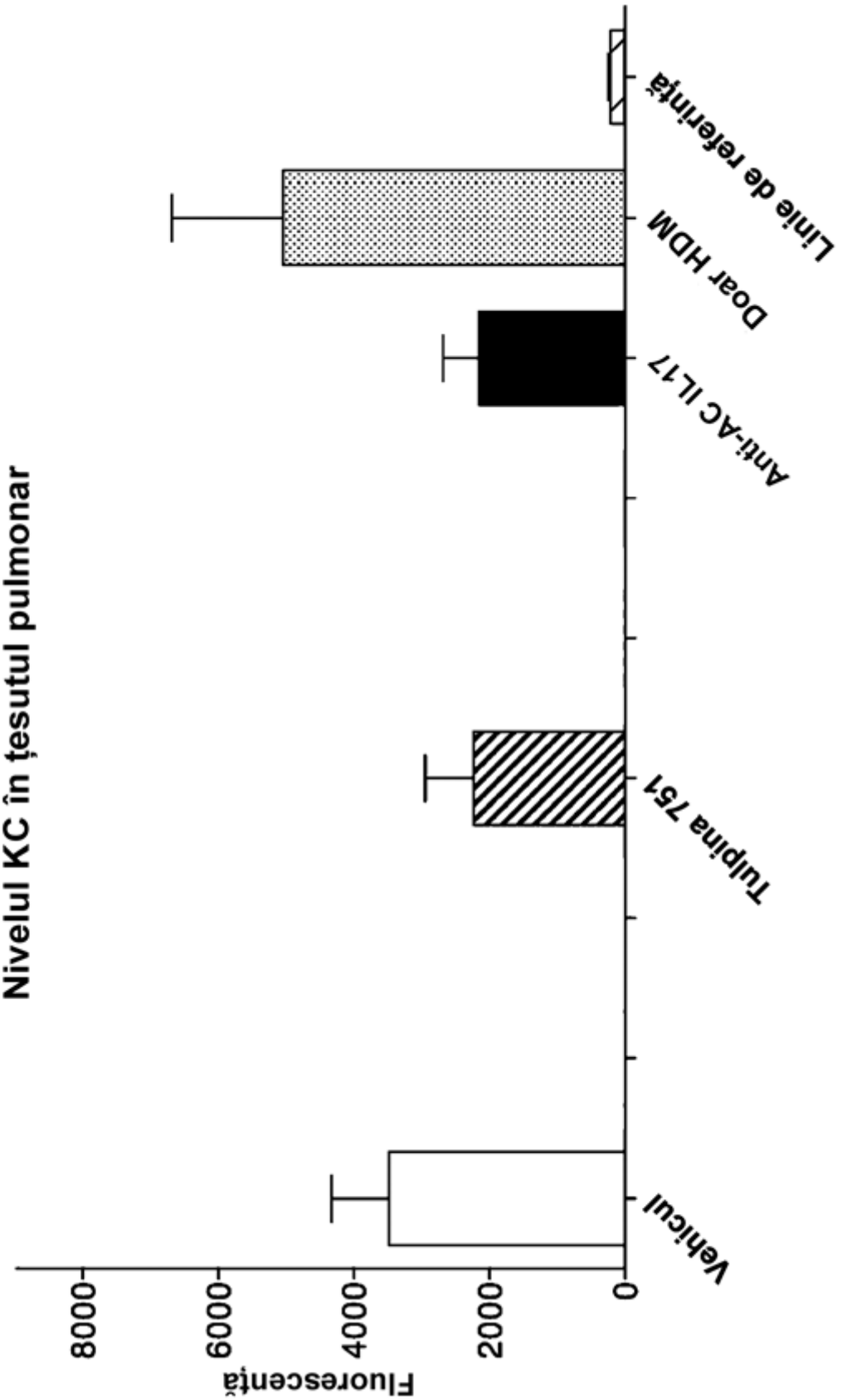


FIG. 62

Nivelul IL-17A în țesutul pulmonar

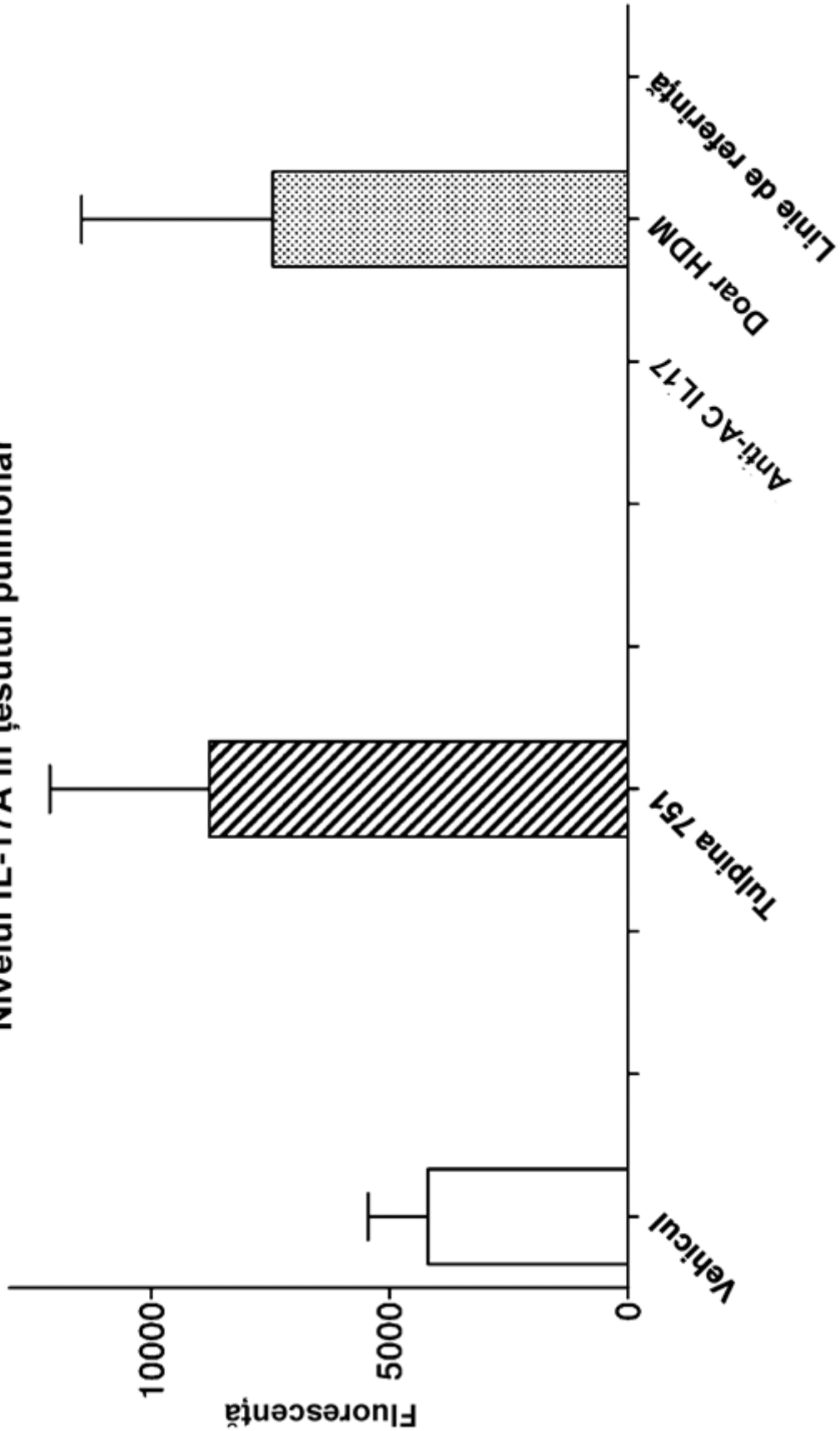


FIG. 63

Nivelul IL-17A în țesutul pulmonar

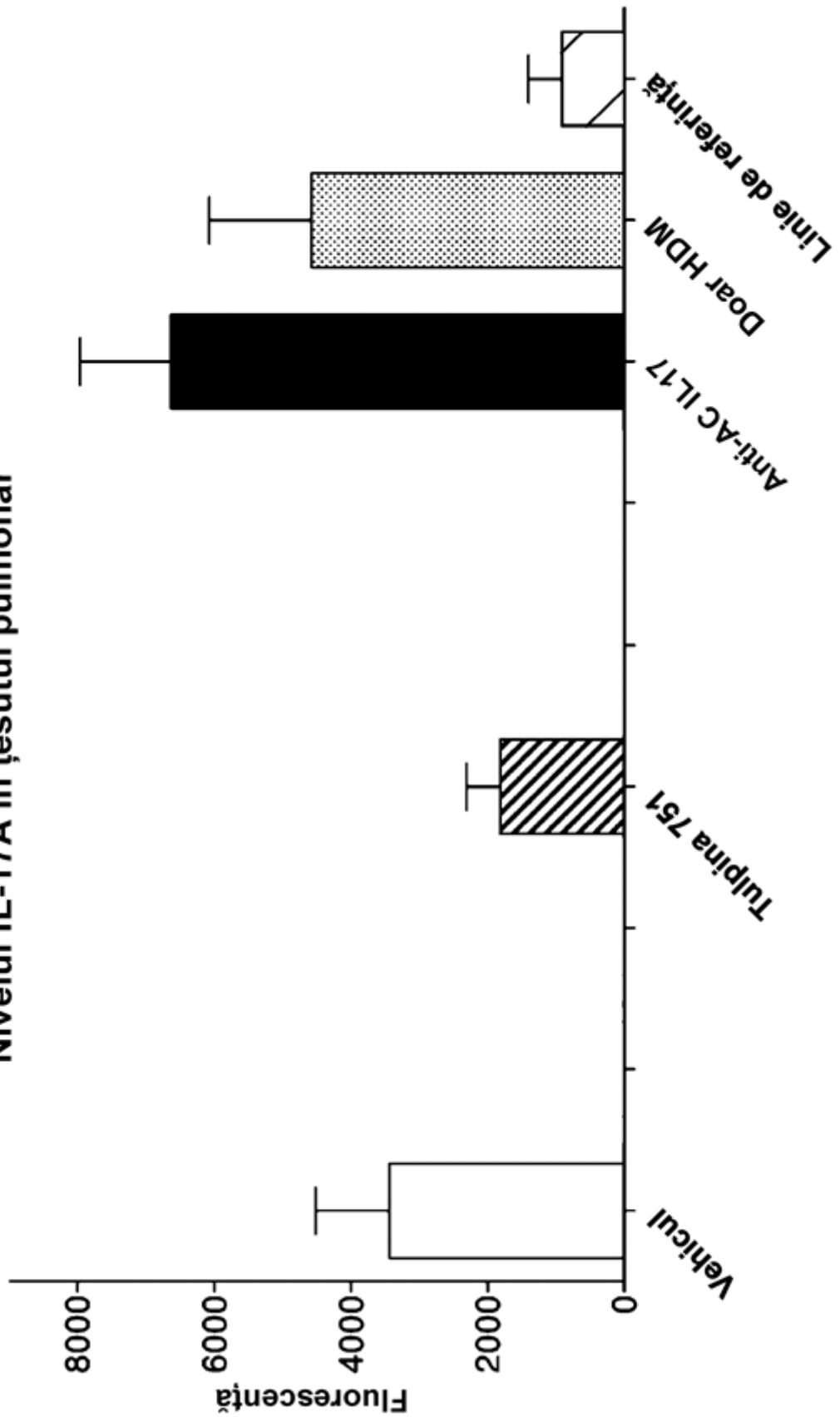
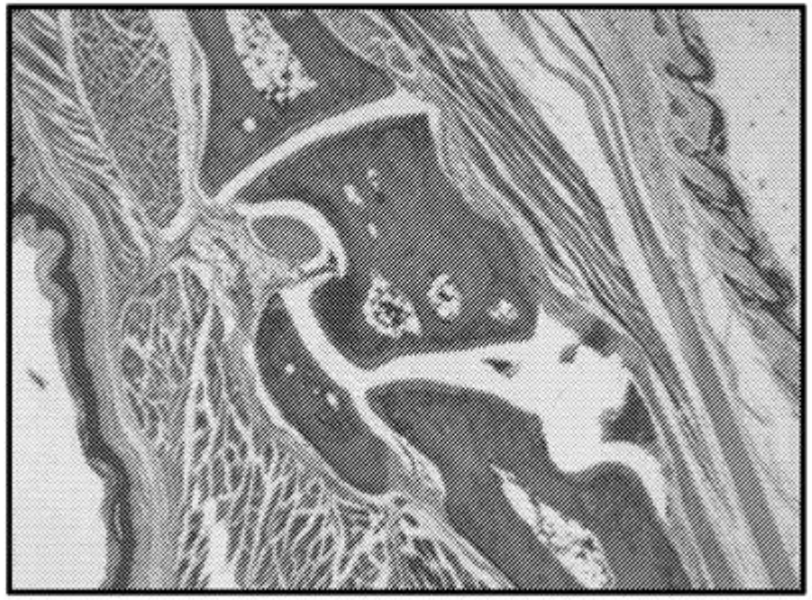


FIG. 64

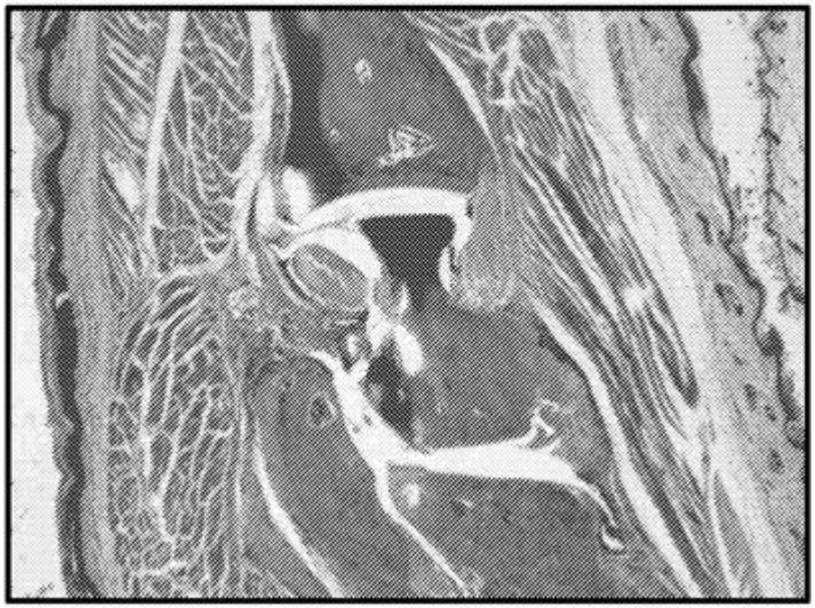
Nivelul IL-33 în țesutul pulmonar

FIG. 65

Model vizual pentru evaluarea histopatologică



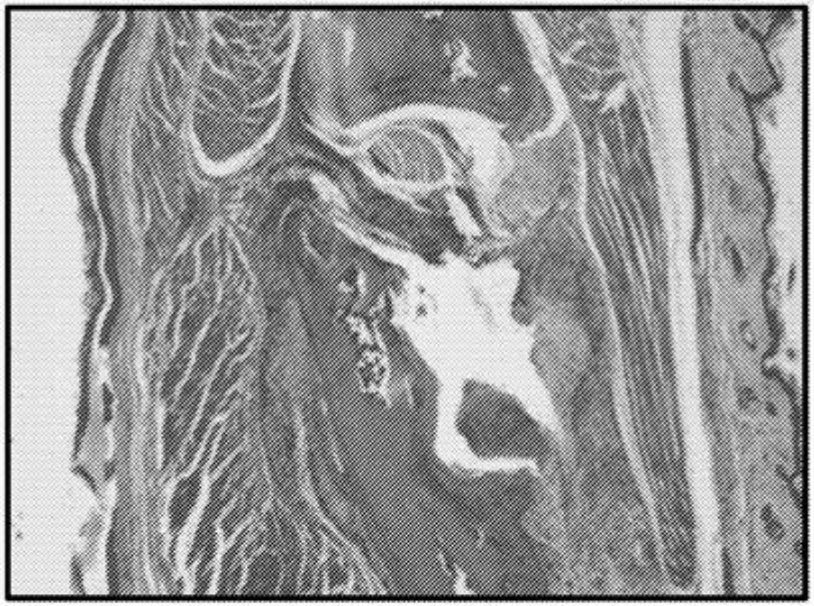
Gradul 0



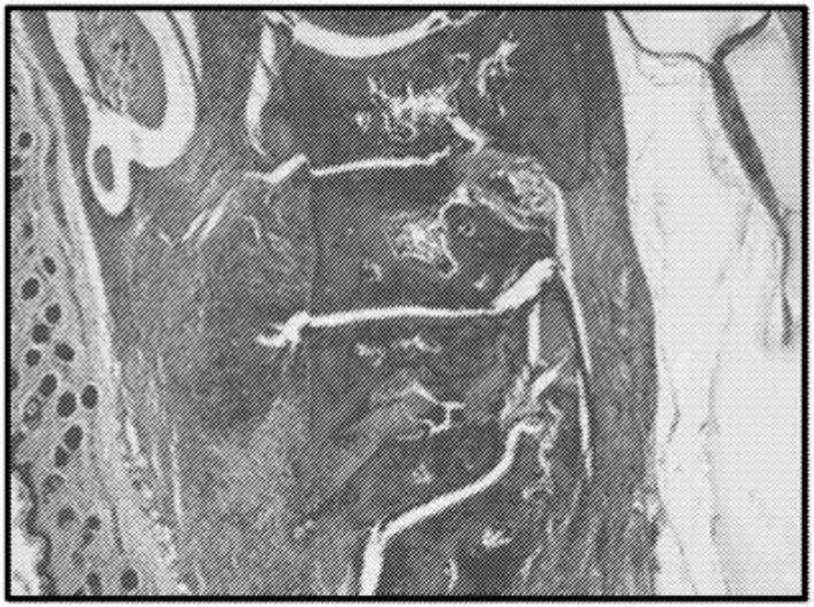
Gradul 1

e 2018 0809

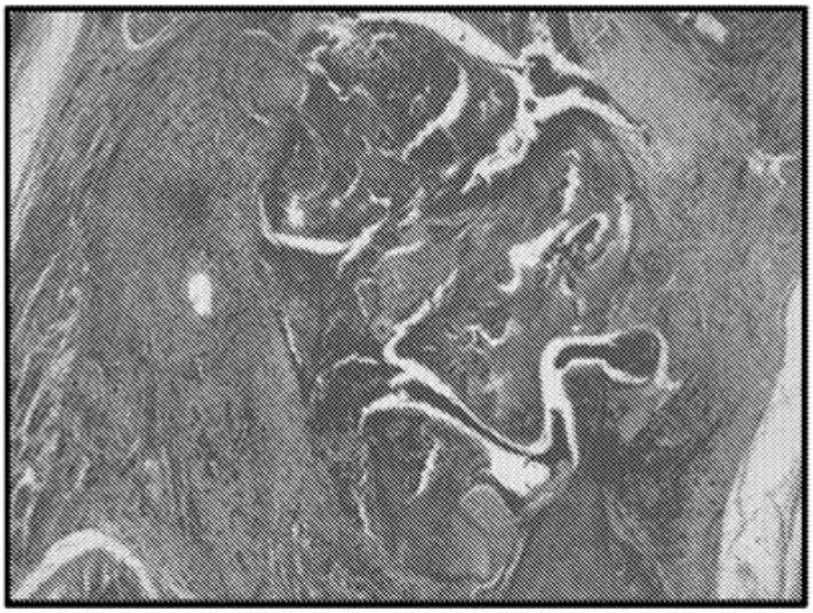
FIG. 65 (cont.)



Gradul 4



Gradul 7



Gradul 9

FIG. 65 (cont.)

FIG. 67

Histopatologie: scoruri ale cartilajului

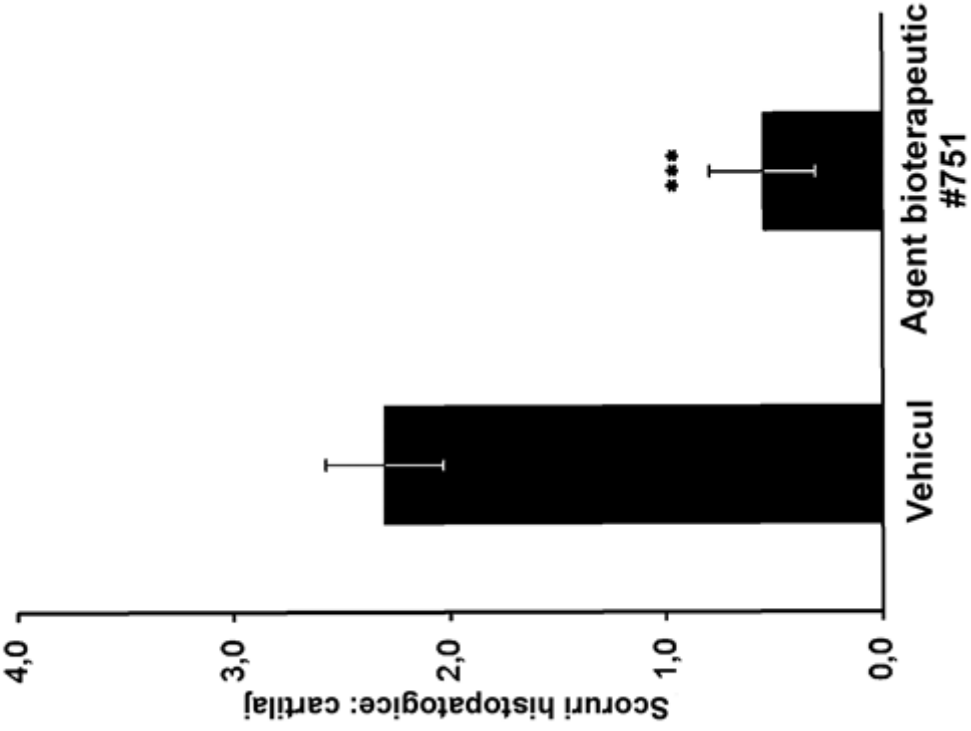


FIG. 69

Histopatologie: scoruri totale

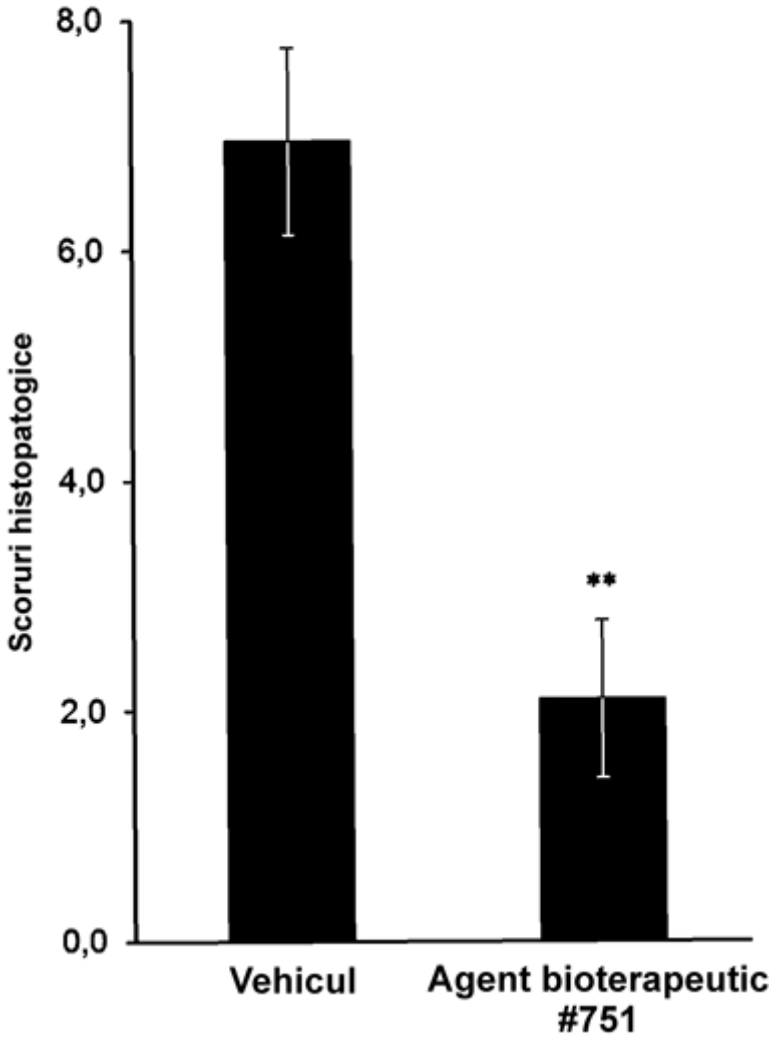
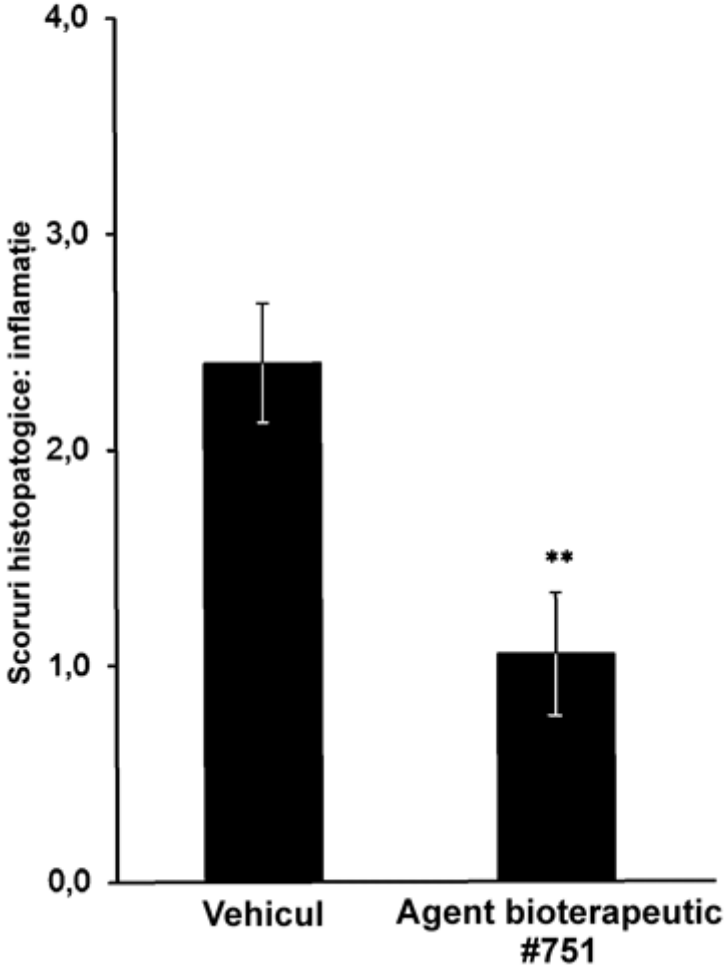


FIG. 66

Histopatologie: scoruri ale inflamației



e 2018 0809

FIG. 68
Histopatologie: scoruri ale oaselor

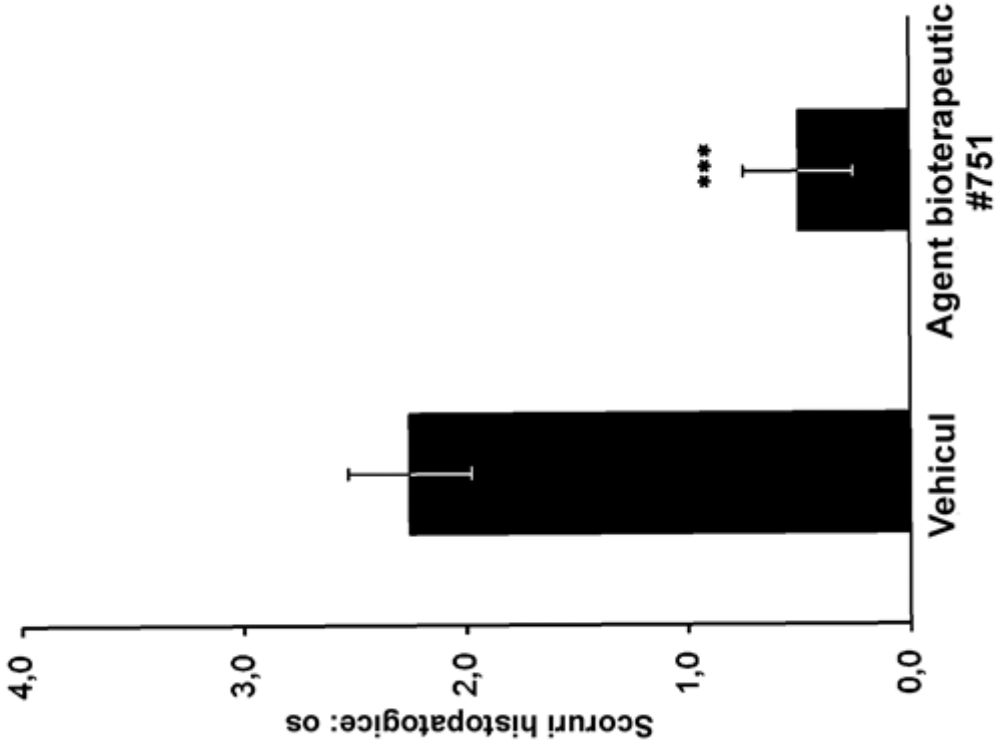
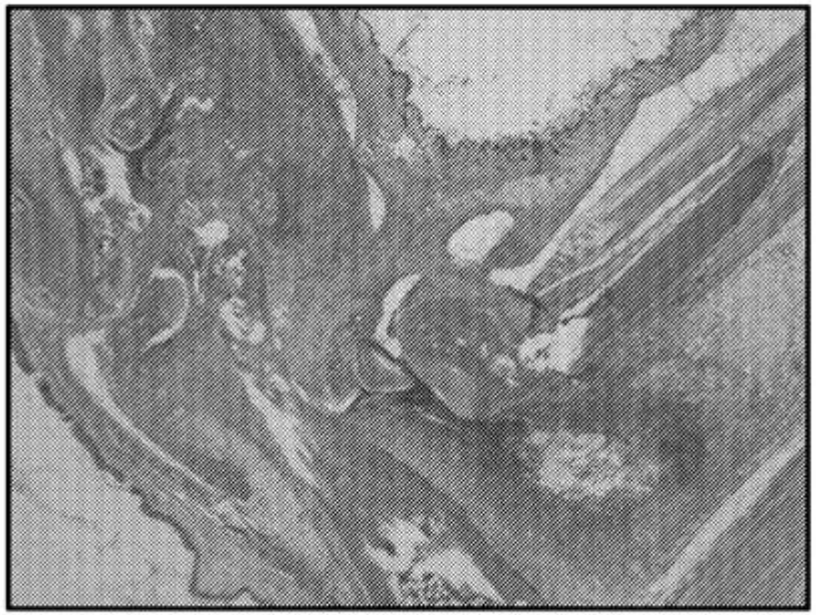
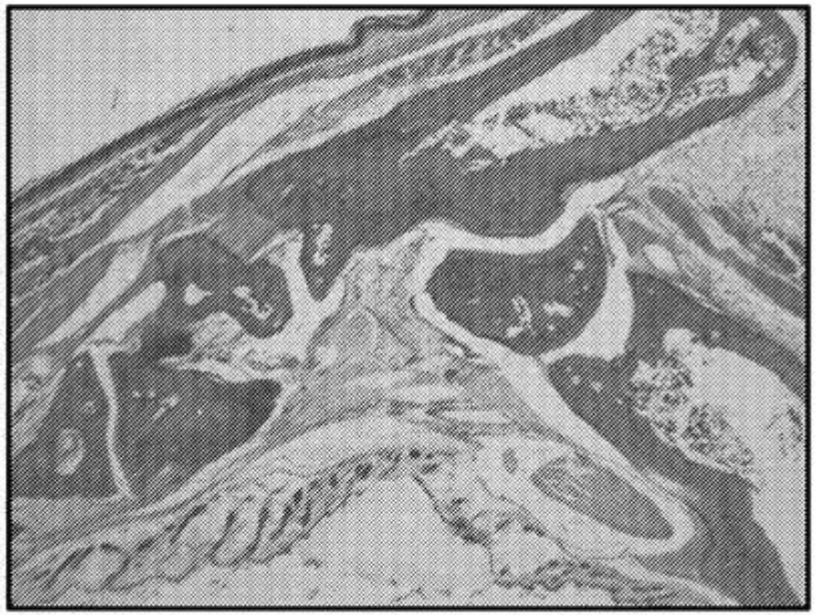


FIG. 70



Vehicul (#1,1 1R, Gradul 9)



Tulpina #751 (#2,R, Gradul 0)

FIG. 71

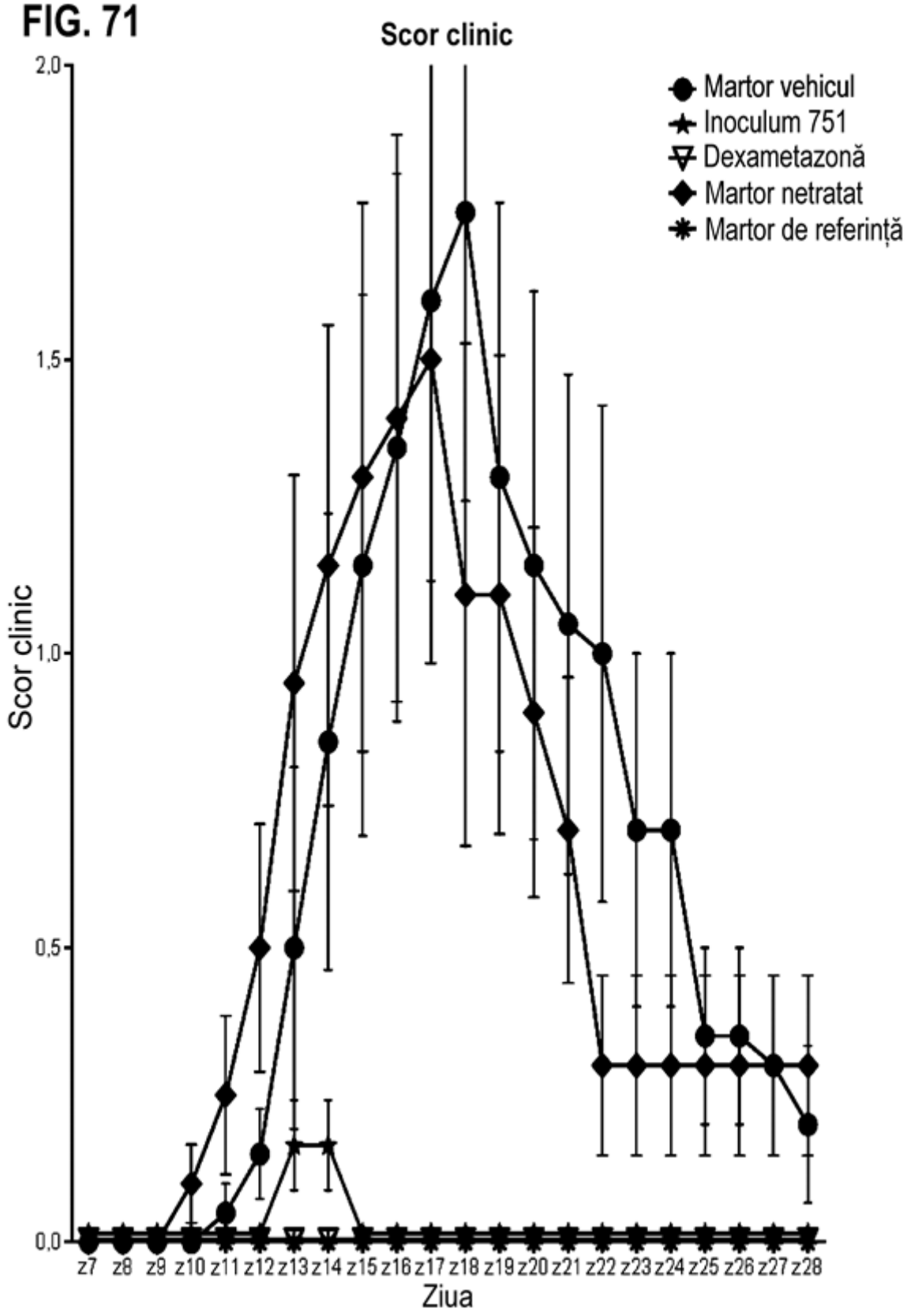

Scor clinic
Martor vehicul
Inoculum 751
Dexametazonă
Martor netratat
Martor de referință
Scor clinic
2,0
1,5
1,0
0,5
0,0
z7 z8 z9 z10 z11 z12 z13 z14 z15 z16 z17 z18 z19 z20 z21 z22 z23 z24 z25 z26 z27 z28
Ziua

FIG. 72

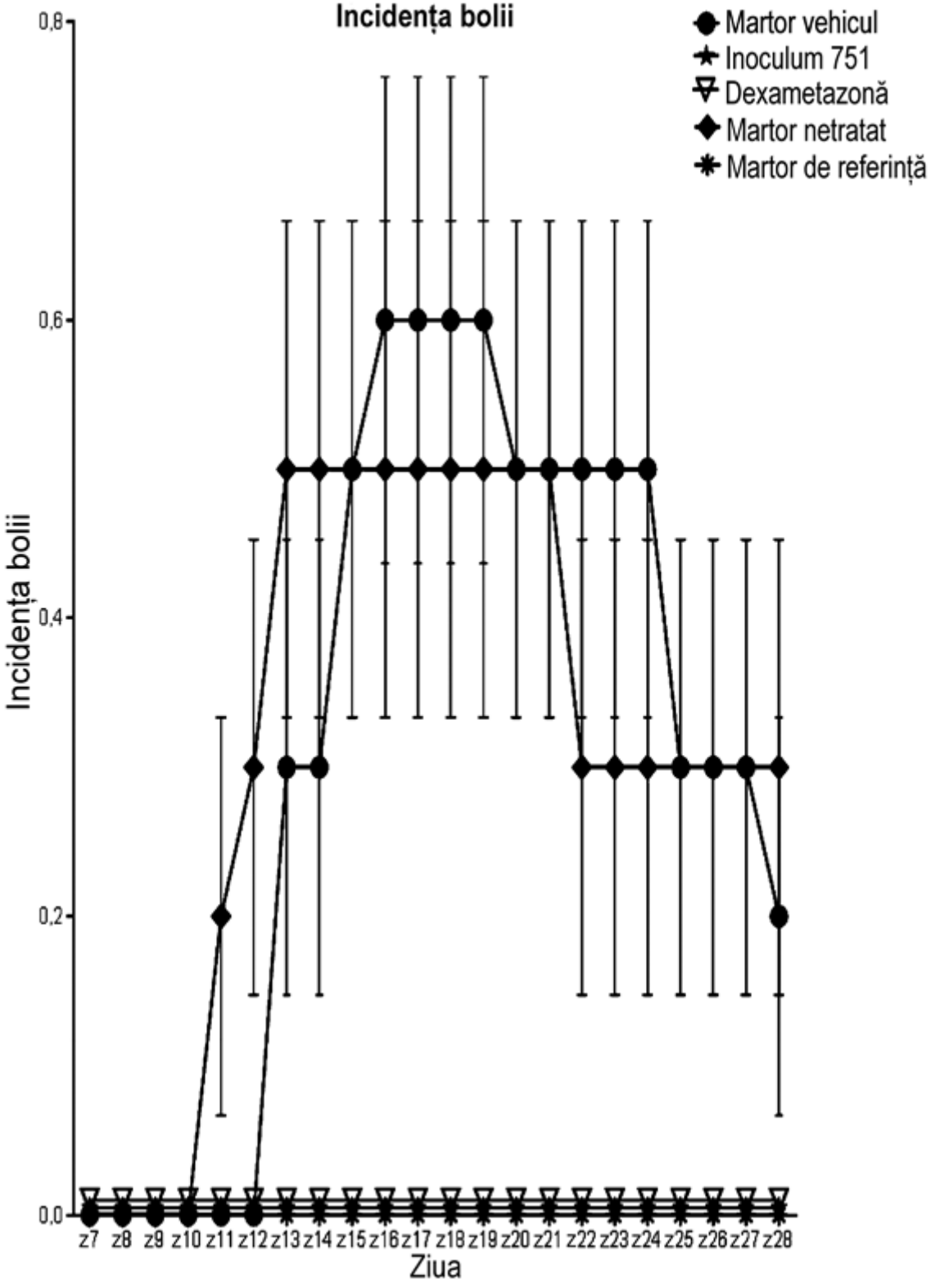

Incidența bolii
Martor vehicul
Inoculum 751
Dexametazonă
Martor netratat
Martor de referință
Incidența bolii
0,8
0,6
0,4
0,2
0,0
z7 z8 z9 z10 z11 z12 z13 z14 z15 z16 z17 z18 z19 z20 z21 z22 z23 z24 z25 z26 z27 z28
Ziua

FIG. 73

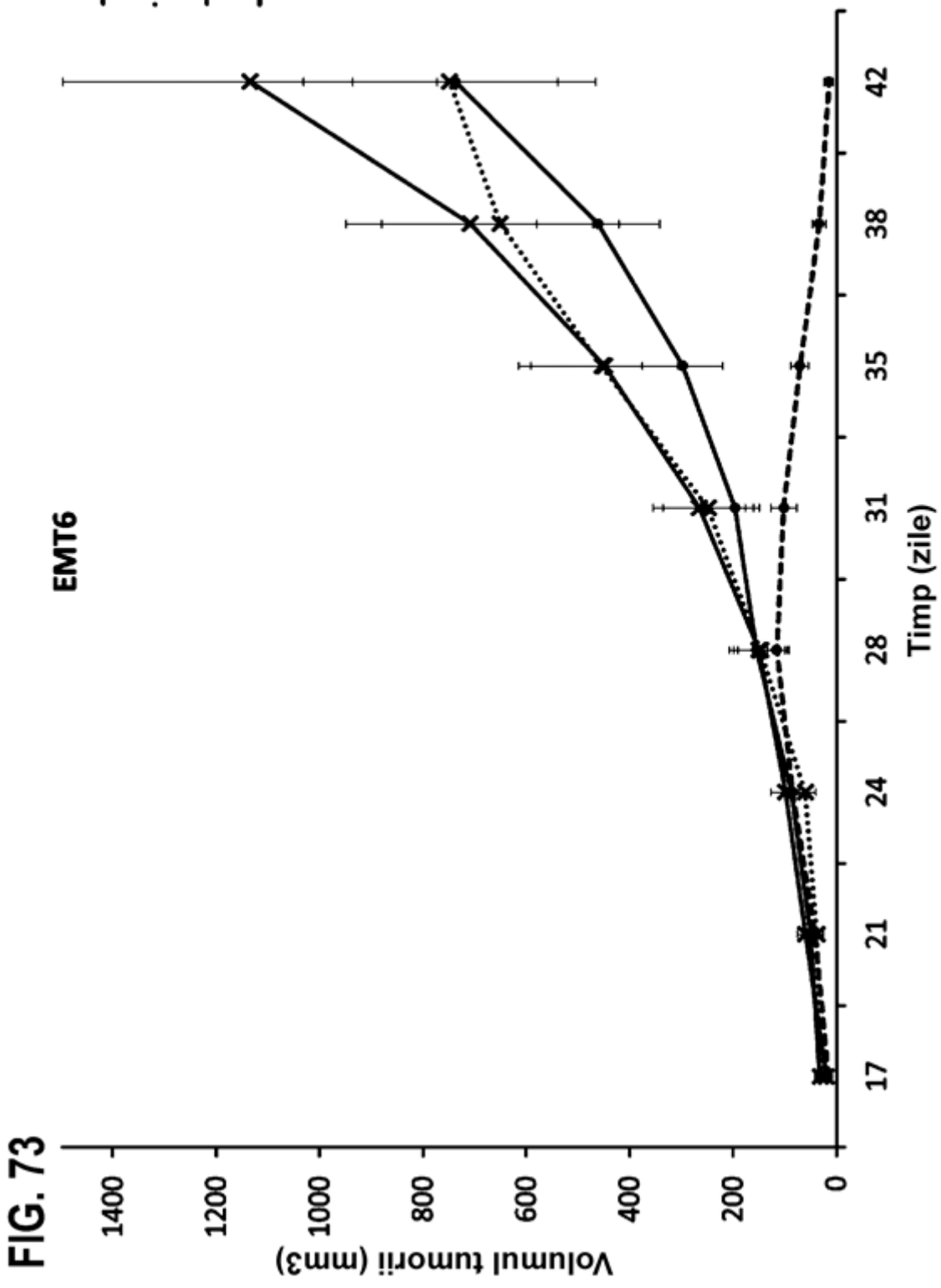

EMT6
Vehicul
Netratat
MRX004
aCTLA4
Volumul tumorii (mm3)
0
200
400
600
800
1000
1200
1400
17
21
24
28
31
35
38
42
Timp (zile)

FIG. 74
LLC

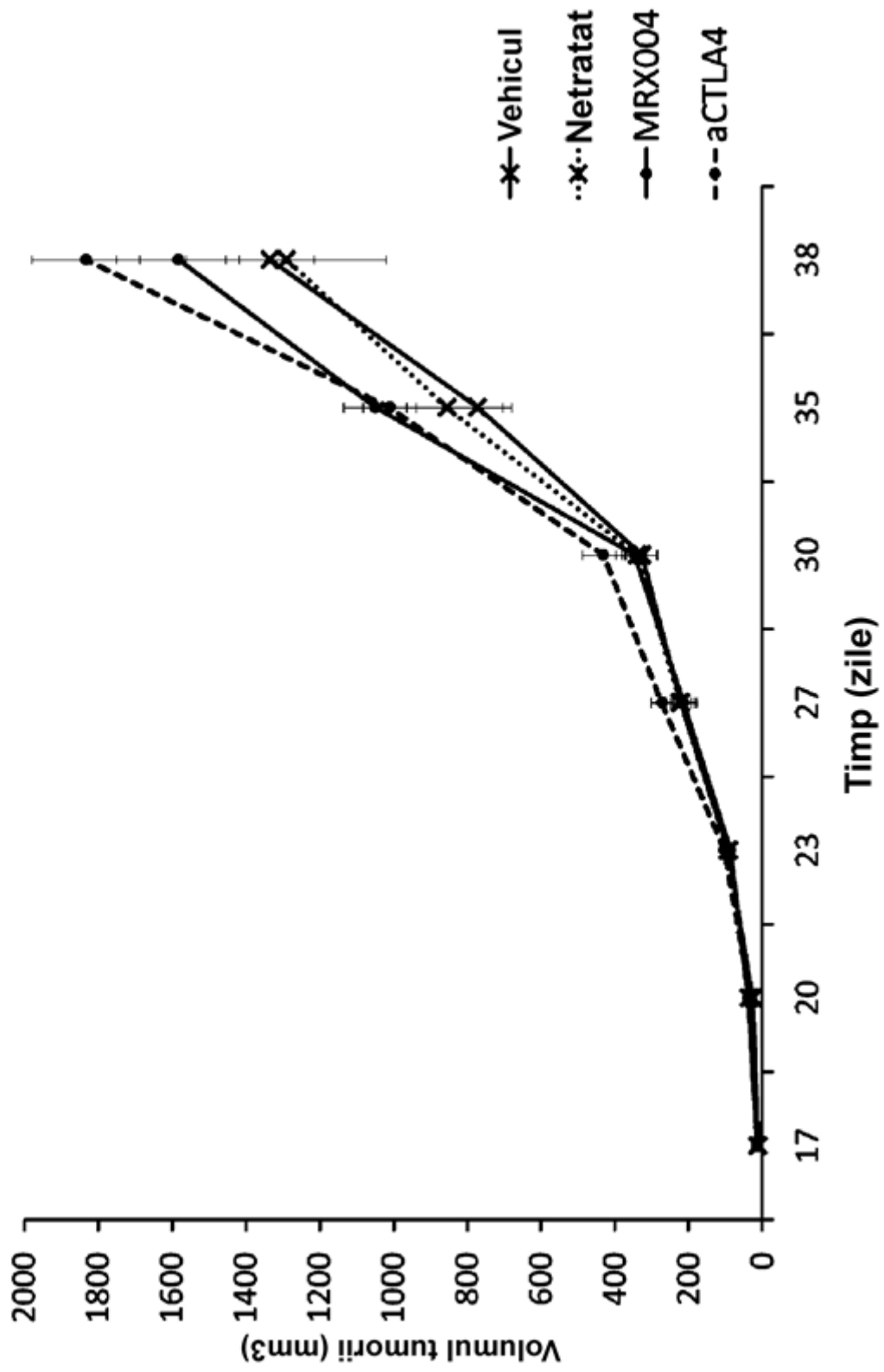
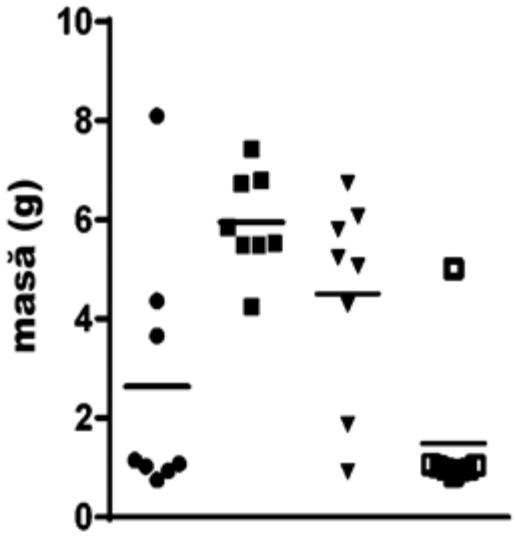

Vehicul
Netratat
MRX004
aCTLA4
Volumul tumorii (mm3)
0
200
400
600
800
1000
1200
1400
1600
1800
2000
17
20
23
27
30
35
38
Timp (zile)

FIG. 75

Masa ficatului la eutanasie (g)



- G1 Netratat
- G2 Vehicul (mediu) PO Q1Dx42
- G4 Tulpină bacteriană #2 (MRX004) 2x10e8bacterii PO Q1Dx42
- G7 Anti-CTLA4 10 mg/kg IP TWx2

FIG. 76 Atașarea la celulele umane

Atașarea în YCFA (2 replicări biologice, normalizate)

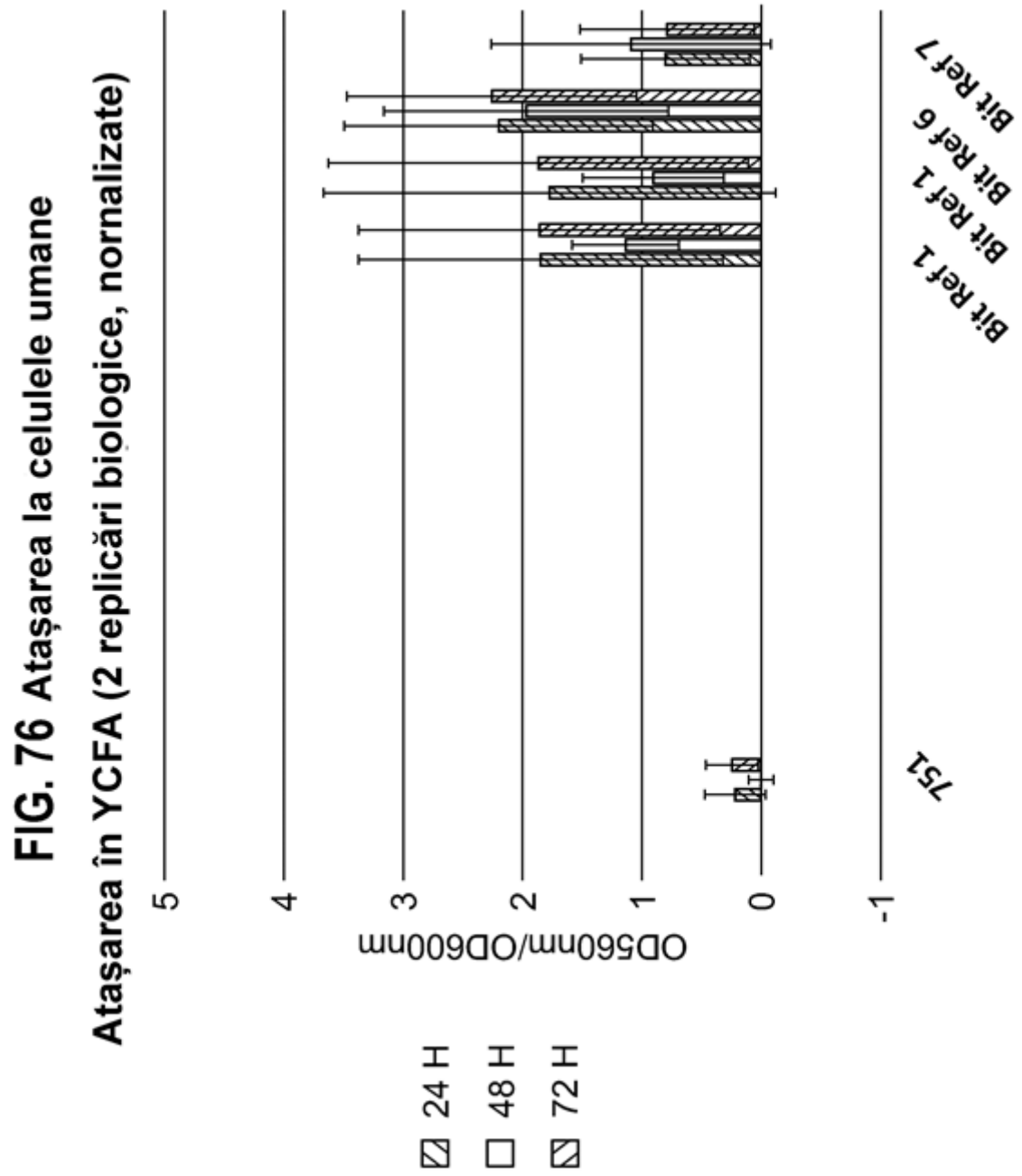


FIG. 76 (cont.) **Atașarea la celulele umane**

Atașarea în YCFA (2 replicări biologice, normalizate)

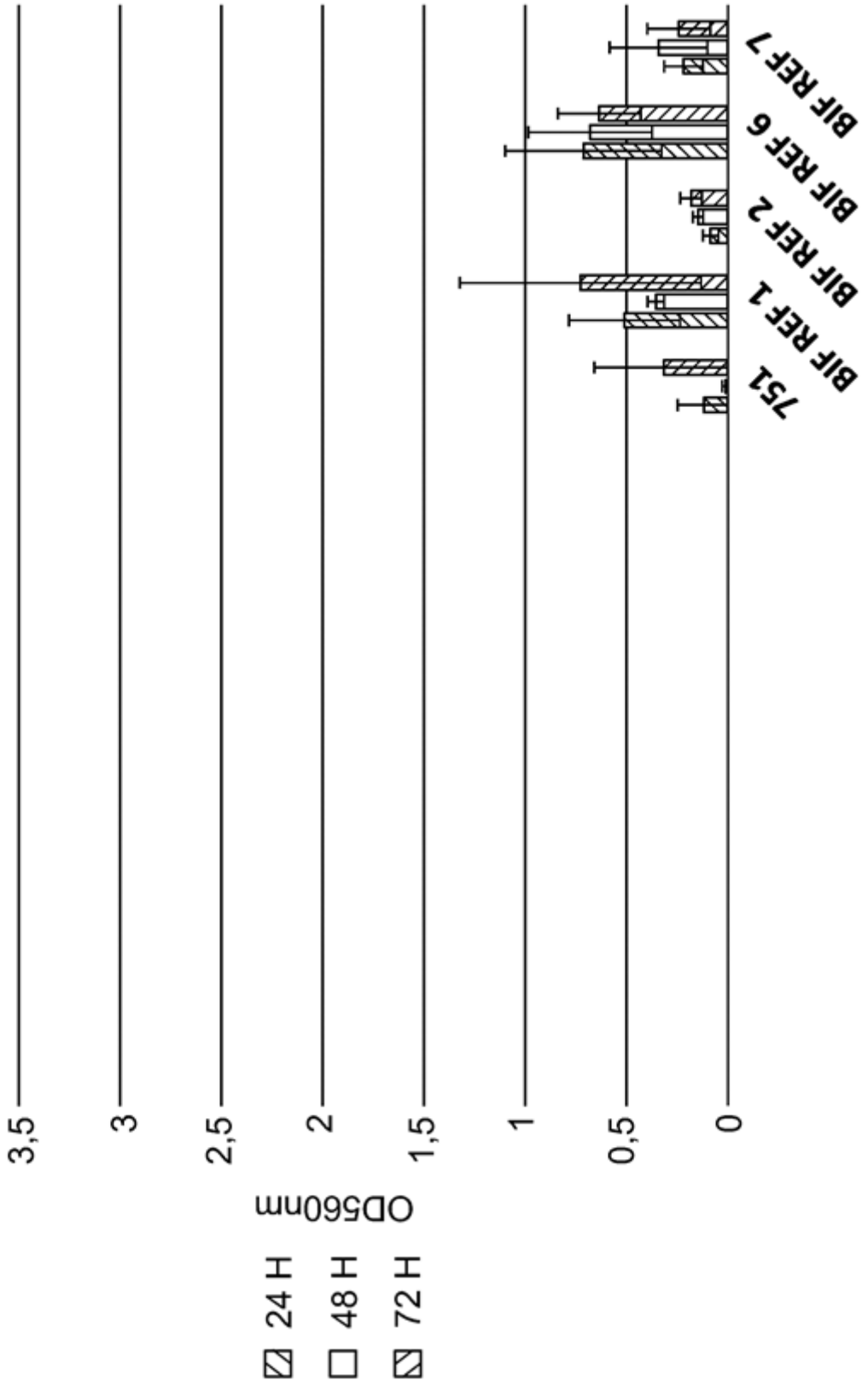


FIG. 77 Producerea de EPS legat

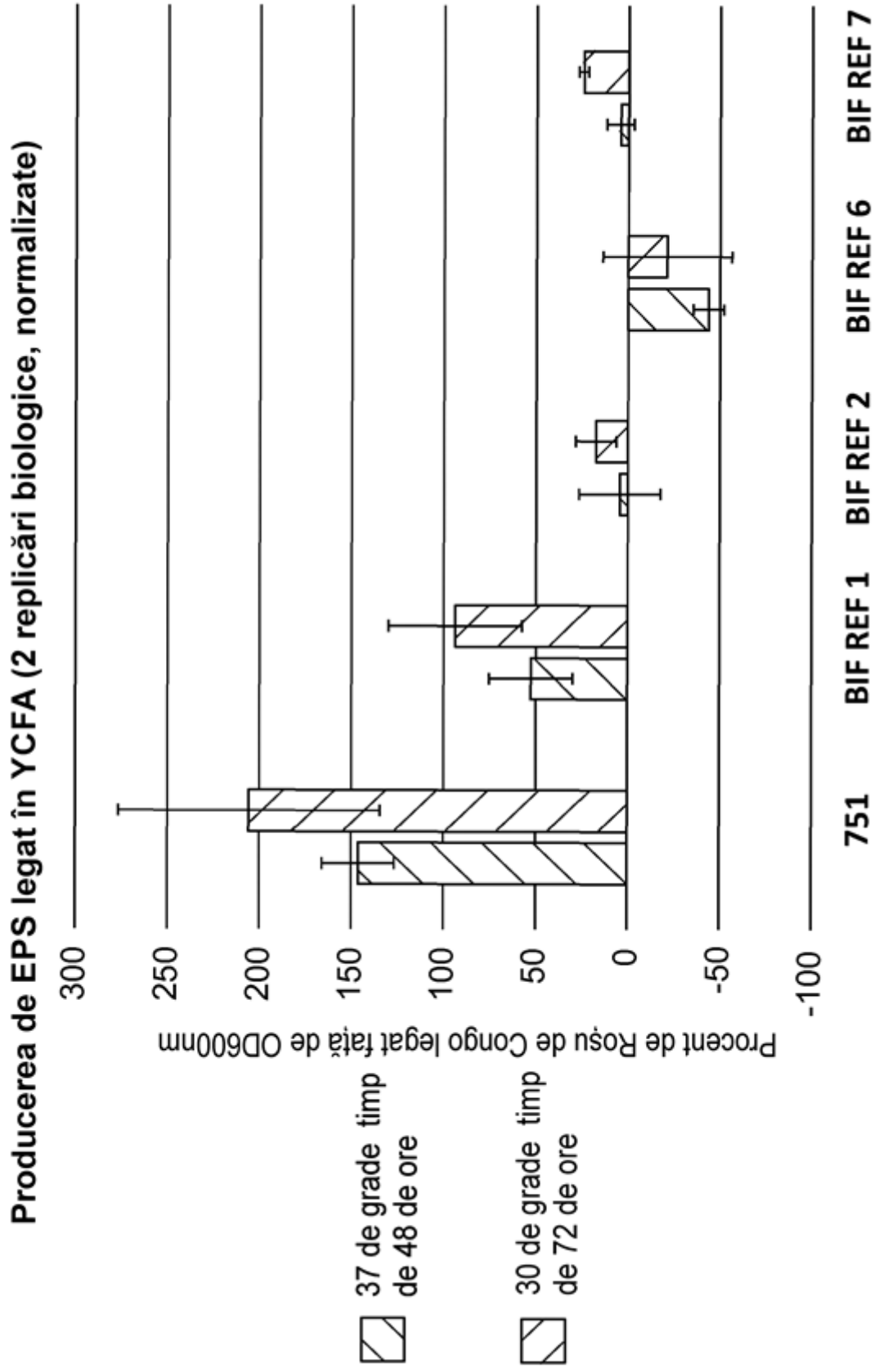


FIG. 77 (cont.) **Producerea de EPS legat**

Producerea de EPS legat în YCFA (2 replicări biologice, normalizate)

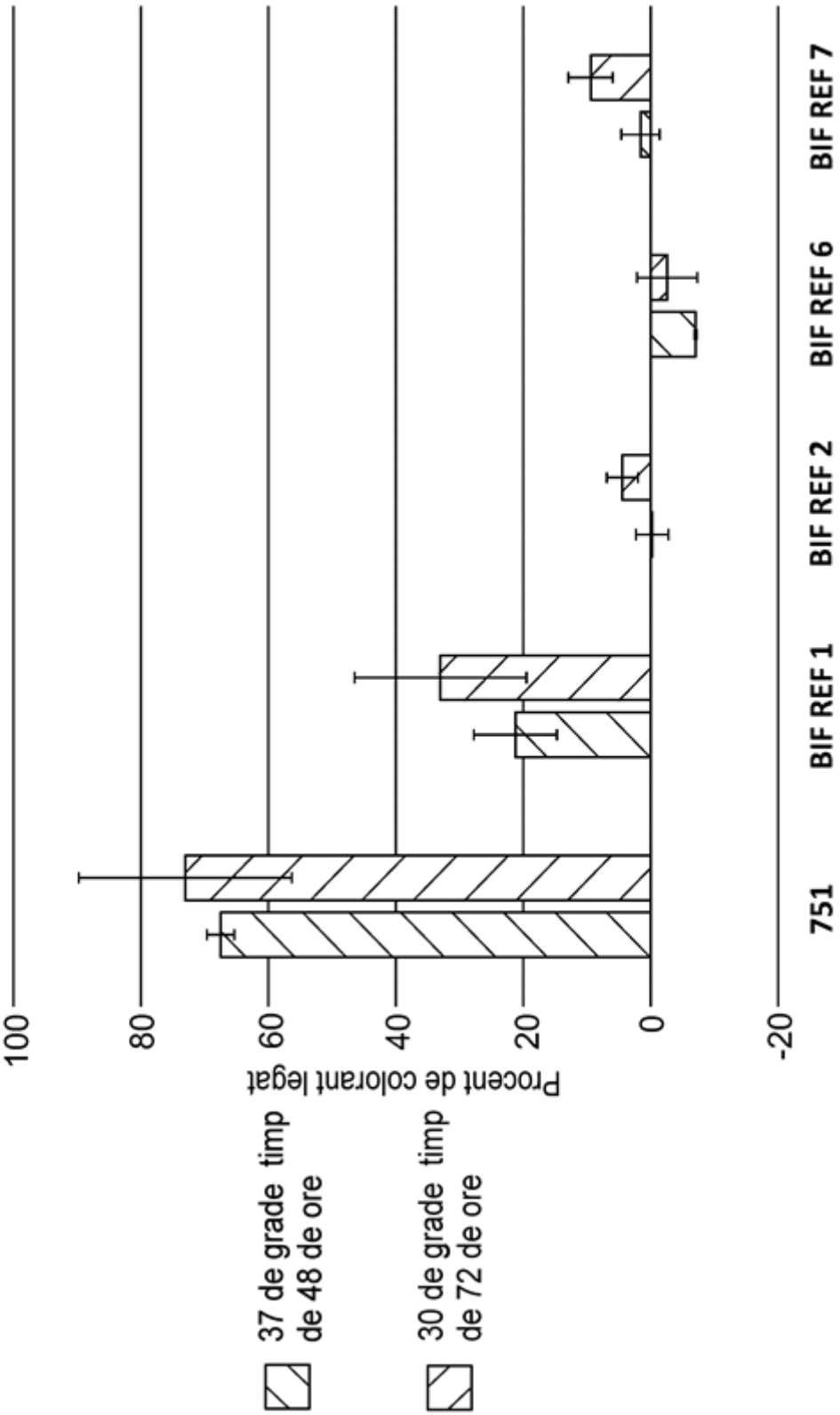


FIG. 78 Producerea de exopolizaharidă legată și eliberată de către MRX004

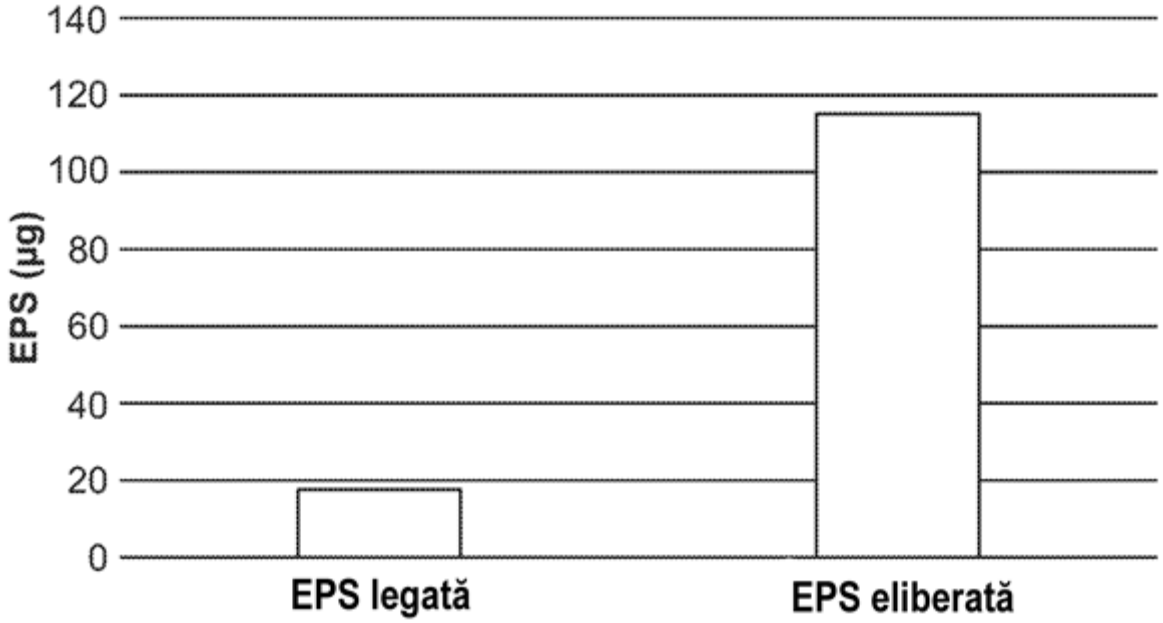


FIG. 79 Atașarea MRX004 la celulele Caco-2

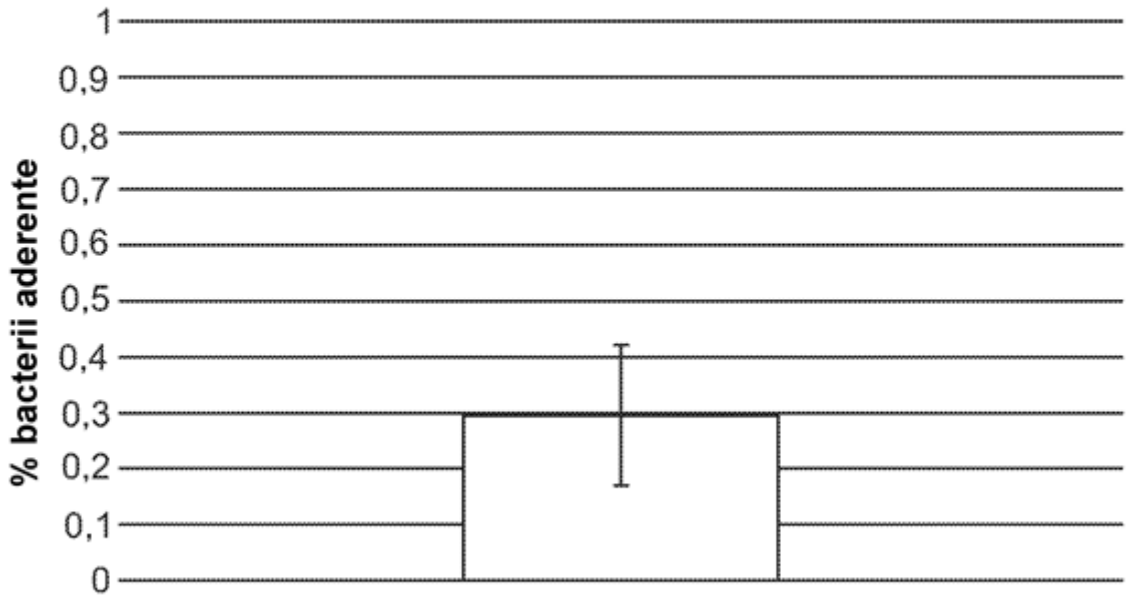


FIG. 80 Profilul ID 32 A rapid al MRX004 față de tulpini de tip *Bifidobacterium breve*

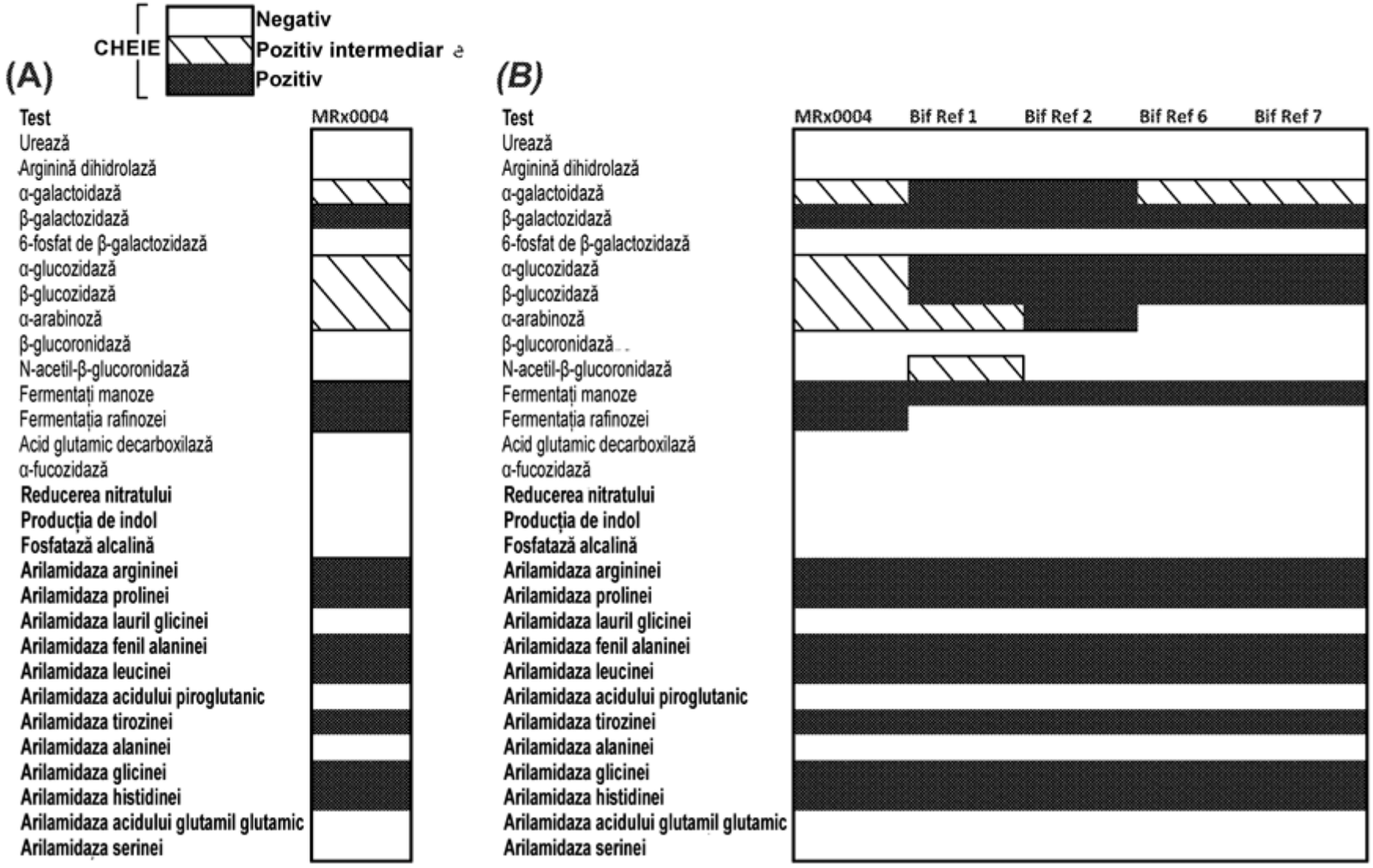


FIG. 81 Analiza API® pe 50 de canale a MRX004